Evaluating Predictors & Interventions in Sphincter of Oddi Dysfunction: The EPISOD Trial

A Phase III Randomized Multicenter Clinical Trial of Sphincterotomy for the Treatment of SOD III Patients

STUDY GROUP CHAIR
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Investigators' Agreement

I have read the attached clinical protocol titled " Evaluating Predictors & Interventions in Sphincter of Oddi Dysfunction: The EPISOD Trial " revised May 01, 2011 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 Digestive Diseases Center at the Medical University of South Carolina and cannot be disclosed to anyone other than members of my staff conducting this trial and members of my Institutional Review Board or Ethical Committee.

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

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Signature of Principal Investigator Date

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Printed name of Principal Investigator

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Signature of Co-Principal Investigator (When applicable) Date

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Printed name of Co-Principal Investigator (When applicable)

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1.0 SUMMARY

Protocol Title	Evaluating Predictors & Interventions in Sphincter of Oddi Dysfunction (SOD)
Acronym	EPISOD
Clinical Trial Phase	Phase III
Study Sites	Six to Ten clinical centers in US
Study Period	Planned enrollment period – 3 years Planned duration of the study – 5 years
Study Population	SOD III Patients
Primary Study Objective	To ascertain whether subjects with SOD III respond to sphincterotomy,
Secondary Study Objectives	To evaluate: • the association between the results of Sphincter of Oddi Manometry (SOM) (abnormal/normal) and the primary outcome (success/failure); • the success rate (as defined in the primary) of subjects who receive biliary sphincterotomy alone versus subjects who receive both biliary and pancreatic sphincterotomy in the subgroup of patients with manometrically proven hypertension of the pancreatic sphincter; • the effects of pre-specified prognostic factors on the primary outcome; • anxiety and depression scores over time and their relation to study outcomes; • the economic impact of SOD III, and of endoscopic sphincterotomy in patients with SOD III; and, to, • the results of a careful follow-up study (EPISOD2) of standard of care treatment (separate protocol).
Study Design	The EPISOD Trial is a two-arm parallel, randomized, double-blinded, sham-controlled, multicenter Phase III clinical trial of endoscopic sphincterotomy as treatment for adults 18 to 65 years of age diagnosed with SOD III.
Sample Size	A minimum of 214 subjects will be randomized using a 2:1 allocation in favor of sphincterotomy and will be followed for 12 months post-randomization.
Inclusion Criteria	1. Patients diagnosed with the clinical syndrome of SOD, as defined by the Modified Functional Biliary Disorders Module of the Rome III criteria. 2. Pain burden of Grade 3 or higher on RAPID

	Questionnaire. 3. Cholecystectomy more than 90 days before enrollment 4. Laboratory Tests: Results of blood tests taken within 1 week preceding the baseline visit and any others available from the preceding 6 months (post-cholecystectomy): ● Direct bilirubin, alkaline phosphatase, amylase and lipase results must be no greater than 2 X the upper level of normal (ULN) ● Transaminase levels can be no more than 3 X upper limit of normal (ULN). 5. Normal abdominal imaging by CT or MR/MRCP with bile duct reported at ≤9mm. 6. Upper endoscopy examination without findings to explain the pain. 7. Pain persisting despite a trial of acid suppressant medications for one month (if tolerated) 8. Pain persisting despite a trial of PRN antispasmodics. 9. Subjects on antidepressants for pain control (not required) should be taking them for a minimum of one month prior to the baseline assessment. 10. Patients with SOD with depressive and/or anxiety disorders who receive psychopharmacologic treatment must be on stable medication dose for at least 6 weeks. 11. The total number of days in the previous 3 months that the subject has taken prescription analgesics due to episodes of abdominal pain is not greater than the total number of days the subject has episodes of pain. 12. Access to a telephone. 13. Must be able to speak, read, and write English. Signed and dated informed consent,
Exclusion Criteria	**Pre-ERCP Criteria:** 1. Prior ERCP treatment. 2. Age < 18 or Age > 65. 3. Pregnancy: Women who are pregnant at the time of Screening* will be excluded from the study. (*Note: Women who become pregnant AFTER the Baseline Visit/ERCP will be allowed to remain in the study for telephone follow-up visits). 4. Prior gastric resection or surgery involving biliary diversion. 5. Prior diagnosis of acute pancreatitis (lipase >3 x ULN) including post-ERCP pancreatitis, or of chronic pancreatitis by radiological imaging, EUS 5 or more criteria, or Cambridge criteria moderate or more on ERCP. 6. Daily use of prescription analgesics over the previous month. 7. Presence of significant psychiatric disorders: a. Lifetime psychotic disorders, bipolar disorder; b. Substance use disorders within 6 months; c. Eating disorders within 2 years d. Moderate & severe depression defined by BDI-II

	cutoff scores total score $\geq$ 22, unless there is evidence of an appropriate assessment of their condition by a mental health professional who has to establish that the patient is being appropriately managed and is clinically stable and/or;, e. Suicidal risk (equal to or greater than "low") using MINI suicide section or a score of greater than 0 on question 9 of the BDI. 8. Any condition that, in the investigator's opinion, makes the subject unsuitable for study participation. **ERCP Criteria:** 1. Pancreas divisum (complete or partial) (known or discovered at study ERCP). 2. Any pathology found at ERCP (except sphincter hypertension). 3. Failed pancreatic manometry.
Study Intervention and Follow-up	Upon randomization, each subject receives either a sphincterotomy or sham procedure. Subjects randomized to sphincterotomy will undergo biliary sphincterotomy if they are found to be PSH negative at the time of randomization. If found to be PSH positive, the subject will be randomized to either biliary or dual sphincterotomy. Each randomized subject will be followed for 12-months from the time of randomization.
Primary Outcome Measure	The primary outcome variable is the overall proportion of subjects experiencing a successful procedure. Success is defined as a RAPID Grade of 1 (mild or no disability) at both 9 and 12-months post randomization. A failure is defined as a subject that has a RAPID Grade 2 or greater at months 9 or 12 post-randomization, or who has been referred for further sphincter procedures during the year, or who has taken any prescription analgesic during months 10, 11 and 12 unless the prescription analgesic is prescribed for pain other than abdominal pain and then for no more than 14 days in months 10, 11, and 12..
Statistical Analysis for Primary Outcome Measure	The primary statistical analysis will develop a logistic regression model with treatment group as the factor of interest and clinical center and SOM (normal/abnormal) as covariates. A chi-square test will be performed to compare the treatment group proportions using a two-tailed significance level of 0.05. The intent-to-treat principle will be used for the primary analysis and is defined as all persons randomized to one of the two interventions.

2.0 OBJECTIVES

2.1 Primary

It is hypothesized that, among persons diagnosed with SOD III, endoscopic sphincterotomy will result in a higher success rate (in terms of pain related disability) than sham treatment. Success is defined as a RAPID Grade of 1 (mild or no disability) at both 9 and 12-months post randomization. A failure is defined as a subject that has a RAPID Grade 2 or greater at months 9 or 12 post-randomization, or who has been referred for further sphincter procedures during the year, or who has taken any prescription analgesic use during months 10, 11 and 12 unless the prescription analgesic is prescribed for pain other than abdominal pain and then for no more than 14 days in months 10, 11, and 12.

2.2 Secondary

1. **Evaluate the association between the results of SOM (abnormal/normal) and the primary outcome (success/failure).** Current practice in referral centers uses the results of SOM to decide whether or not to perform sphincterotomy of the biliary and/or pancreatic sphincter. This is based on extrapolations from sparse literature in patients with SOD types I and II.
2. **Evaluate the success rate (as defined in the primary) of subjects who receive biliary sphincterotomy alone versus subjects who receive both biliary and pancreatic sphincterotomy in the subgroup of patients with manometrically proven hypertension of the pancreatic sphincter.** SOM may show abnormalities in either the biliary or pancreatic sphincter, or both. Biliary sphincterotomy is the most common treatment, which may sometimes also reduce pancreatic sphincter pressure. Whether or not to perform pancreatic as well as biliary sphincterotomy is controversial. Since pancreatic sphincterotomy is practiced only in expert centers and carries greater risks, this is an important question.
3. **Evaluate the effects of pre-specified prognostic factors on the primary outcome.** These factors include age, gender, Body Mass Index (BMI), details of clinical history and pain patterns, and presence of other functional disorders. Patients with SOD often have other digestive disorders, such as irritable bowel syndrome, and psychiatric psychopathology, such as anxiety and depression. The impact of these factors on treatment outcome is unknown.
4. **Evaluate anxiety and depression scores over time and their relation to study outcomes.** Since both SOD III and anxiety/depressive symptoms may be influenced by common neurochemical mediators, the change over time in these variables will be explored.
5. **Evaluate the economic impact of SOD III, and of endoscopic sphincterotomy in patients with SOD III.** SOD III is a common and costly condition where an effective early treatment may be expected to increase quality of life (QOL) and possibly reduce the cost of subsequent medical care to justify and/or offset the upfront cost and risk of ERCP. This analysis will allow us to estimate expected differences in health care costs over the first year, and differences in patients' value of their QOL over 12 months for all patients.

3.0 BACKGROUND AND RATIONALE

3.1 Background of Disease

3.1.1 Sphincter of Oddi Dysfunction

Sphincter of Oddi dysfunction (SOD) encompasses a spectrum of disorders in which stenosis or spasm of the biliary and/or pancreatic sphincters result in episodes of abdominal pain. The diagnosis is often considered in patients with biliary/pancreatic-type pain who have previously undergone cholecystectomy, and in those who suffer from recurrent idiopathic pancreatitis. More than half a million cholecystectomies are performed annually in the United States, and 10-20% of these patients present afterwards with continuing or recurrent pains (Steinberg, 1988; Varadarajulu and Hawes, 2003). About half of these patients will have some objective findings on laboratory studies or imaging (e.g. abnormal liver enzymes, or a dilated bile duct), and are categorized by the Milwaukee classification (Hogan and Geenen 1988, Petersen 2004[1], Petersen 2004[2], Sherman and Lehman, 2001; Varadarajulu and Hawes, 2003) as SOD Types I and II. Many of these patients are found at endoscopic retrograde cholangiopancreatography (ERCP) to have bile duct stones or fibrotic sphincter stenosis, and are effectively treated by standard endoscopic biliary sphincterotomy.

Patients who have similar symptoms, but who have no significant abnormalities demonstrated on standard imaging and laboratory tests, are categorized as SOD III, with the supposition that episodes of pain are due to intermittent sphincter dysfunction. These patients are very difficult to evaluate and to manage effectively (Cohen et al, 2002), not least because there are no objective markers of the condition. Indeed some gastroenterologists are skeptical of its existence, or assume that it is only a small part of a broader problem of motility disturbance or visceral hypersensitivity (Kellow et al., 1999). Fortunately, the diagnostic problem has been helped recently with a publication of the comprehensive ROME III criteria for diagnosis of biliary and other functional gastrointestinal disorders (Behar et al, 2006, Drossman). SOD and other digestive dysfunctions are clearly defined on clinical grounds (certain patterns of pain and disability), in the absence of detectable structural disease.

Patients with clinically defined SOD III (at least those with severe symptoms) are often sent to tertiary centers for further evaluation. This usually involves ERCP to check that there are no subtle structural abnormalities in the papilla, biliary tree or pancreas (e.g., small stone, tumor or pancreas divisum), and to allow performance of Sphincter of Oddi manometry (SOM) (Viceconti and Micheletti, 1995; Petersen 2004[1]). SOM involves placing a pressure-sensing catheter into the bile duct and/or pancreatic duct, to record the basal sphincter pressure in each segment of the sphincter. The results of SOM are used to decide whether to perform sphincter ablation (at the same ERCP examination), by endoscopic sphincterotomy of the biliary and/or pancreatic sphincters. SOM is not widely

available, and is not consistently predictive of the results of sphincterotomy. Published series are small, and different SOD types are often mixed together (Botoman et al,1994; Park et al,2003; Petersen 2004[2]; Piccini etr al., 2004). In general it appears that endoscopic biliary sphincterotomy provides benefit in 70% of these patients, at most. A recent large surgical series of sphincteroplasty claimed good or excellent results in 87%, but included a variety of patients, and the outcome measures were not clearly defined (Madura et al., 2005. The endoscopic approach is less morbid than open surgery, but still carries significant risks. Belief in SOM as a gold standard for the diagnosis of SOD is not well founded, particularly in this group of patients. Limited studies in patients with SOD Type II (pain with some objective abnormalities suggesting biliary disease) have shown that the results of SOM are somewhat predictive of the outcome of biliary sphincterotomy (Geenen et al., 1989; Toouli et al., 2000). These results have been extrapolated in practice to patients with SOD III, without scientific justification. These patients are different, since there are no objective findings (biochemical or imaging) to prove or suggest that the problem is primarily in the biliary/pancreatic area. Furthermore, the reproducibility of SOM is not well established (Varadarajulu et al 2003; Thune et al, 1991; Petersen, 2004). Another problem is that ERCP with SOM can cause pancreatitis in up to 20% of patients (Sherman and Lehman, 2001; Viceconte and Micheletti, 1995; Sherman et al, 1991; Chen et al., 1994; Freeman and Guda, 2004). This risk has recently been reduced, but not eliminated, through the routine use of temporary pancreatic stenting (Tarnasky et al., 1998; Jacob et al., 2001; Fogel et al., 2002; Tarnasky 2003). Sphincterotomy also carries risk of other severe complications such as bleeding and perforation, and the possibility of delayed stenosis (Sherman et al, 1991; Cotton et al., 1991; Chen et al., 1994; Freeman et al., 1996; Kalloo and Pasricha, 1996; Varadarajulu and Hawes, 2003).

Many patients suspected of having SOD also have symptoms of more generalized digestive dysfunction (e.g. irritable bowel syndrome). Whether or not their presence affects the results of treatment aimed at the sphincter has not been established. An important factor confusing assessment of the results of treatment is the powerful placebo effect of endoscopic intervention. These patients are often anxious, and sometimes desperate, when they reach tertiary referral centers. Studies with sham arms have shown placebo responses in 24% (Sherman and Lehman,2001), and 38% of patients (Geenen et al,1989;Toouli et al, 2000; Petersen 2004[1], Petersen 2004[2]).

Since the benefit/risk ratio of ERCP/SOM/sphincterotomy is less than ideal, efforts have been made to develop less invasive methods for investigation and management. Alternative diagnostic approaches have included morphine-prostigmine provocation tests, dynamic isotope studies, and changes in bile duct diameter on scans after stimulation with fatty meals or cholecystokinin (CCK) (Craig et al., 2003; Sostre et al., 1992; Hogan 2002). There have been trials of medical therapy, such as calcium channel blocking agents and injection of Botulinum toxin (Khurooet al., 1992; Hogan, 2002; Wehrmann et al, 1998; Pasricha, 1994; Rosenblatt et al., 2001; Topazian et al., 2003; Petersen 2004[1]). Despite a few encouraging reports, these modalities have not proven to be effective generally, and are not widely used (Varadarajulu and Hawes, 2003; Pineau et al., 2001; Petersen 2004[2]).

Patients categorized as SOD III can have disabling episodes of pain with significant impact on their quality of life (QOL), but the condition itself is not life-threatening. Most patients are relatively young and healthy, precisely the

patients in whom ERCP interventions carry the greatest risk (Freeman et al., 2001; Cotton 2001), a fact emphasized at the NIH State-of-the-Science Conference on ERCP (Cohen et al., 2002). Some of these patients are now being treated in community practice with ERCP and empiric sphincterotomy (without SOM), which is speculative at best, and dangerous at worst.

All of these facts mandate the need for a blinded, sham-controlled evaluation of sphincterotomy, along with a blinded evaluation of the predictive value of SOM and other possible predictors.

3.1.2 Assessment of Pain, Disability and Changes with Treatment

Patients with SOD III suffer from intermittent episodes of abdominal pain that are moderate to severe in intensity. Pain episodes often interfere with ability to function in primary roles (e.g., work, homemaker, etc). Available interventions attempt to reduce pain and associated disability. However, measurement tools have not been developed to reliably and validly track these outcomes in patients before and after intervention. To advance work in this area, we have spent the last three years exploring and testing different methods.

Many pain assessment instruments, such as the McGill Pain Questionnaire and the Brief Pain Inventory, have been validated and are widely used in the context of frequent or continuous daily chronic pain, e.g. due to cancer (Kane et al.,2002; Katz and Melzack,1999). These instruments are not suitable for patients with suspected SOD, who typically suffer from severe short-lived episodes of pain that are unpredictable, and vary in both severity and frequency. Two validated instruments for assessing the status of patients post-treatment were considered for the assessment of SOD III patients; a visual analogue scale (VAS) for pain (Carlsson, 1983), and the Patients Global Impression of Change (PGIC) which has been validated in other disease states and designed to measure overall improvement relative to a baseline (Guy, 1976; Farrar et al., 2001). The PGIC asks the patient (post-treatment) whether they are 1) Very Much Improved, 2) Much Improved, 3) Minimally Improved, 4) No Change, 5) Minimally Worse, 6) Much Worse, or 7) Very Much Worse. The VAS is of concern since it does not include assessment of disability, which is of key relevance to the outcome of these patients. The PGIC is of concern due to recall bias over a 12-months follow up period. A 'pain-volume' scale i.e. days of pain episodes in a month multiplied by the average severity of the reported episodes, was also considered, but again the concept does not include assessment of disability. Daily/weekly diaries of pain and disability were considered but compliance would be a problem over a 12-month period since the pain episodes are intermittent, and patients may be inconsistent in reporting their number, frequency and severity.

The investigators studied the extensive literature on measurement of pain and resulting disability, including scientific articles (McDowell and Newell,1996; Katz and Melzack,1999; Landrum and Welch,2000; Farrar,2000; Von Korff et al.,1992) and recent comprehensive reviews, such as the recommendations of the IMMPACT group (Initiatives on Methods, Measurement and Pain Assessment in Clinical Trials) (Dworkin et al, 2005). They corresponded with numerous published authorities, including J. Ware, R. Melzack,. C. Sherbourne, R. Lipton, M Von Korff, J Farrar, R Portenoy, C Cleeland, M Lewandowski, R. Dworkin and S. Fishman, and searched for validated scales that had been developed for assessment of other intermittent pains and disabilities, such as backache and

arthritis (Beursken et al.,1996; Goldsmith et al.,1993). The investigators discussed using the SF-36 instrument as the primary outcome measure but this was deemed to be too general and not sufficiently disease-specific. Investigators at the Medical University of South Carolina validated and published a Digestive Disease Quality of Life measure (DDQ15) but this instrument covers patients with many digestive diseases, and has not yet been used in practice (Hebert et al, 2001).

The closest analogy to pain and disability experienced by SOD III patients is in the field of research in migraine headache. Like SOD pain episodes, migraine headaches are unpredictable, intermittent, and temporarily disabling. The MIDAS (Migraine Disability Assessment) questionnaire measures headache-related disability as lost time due to headache from paid work or school, household work or non-work activities over the prior 3-months, and defines four levels (Grades) of disability ranging from 'little or no disability' to 'severely limiting disability' (Lipton et al,2001; Stewart el al, 2001 – see Appendix D). The investigators have had extensive discussions with the co-developer of the MIDAS, Dr. Walter 'Buzz' Stewart, who has advised about appropriate pilot studies (below), and who is a consultant to this study (see Letter of Support). Together, the team has developed the RAPID instrument (Recurrent Abdominal Pain Intensity and Disability) based on the MIDAS terms and concepts. A series of 5 questions, completed by the patient, records lost time due to abdominal pain episodes from paid work or school, household work or non-work activities over the prior 3-months. An additional two questions ask the average frequency and severity of the episodes of abdominal pain on a 3-month recall basis (See Appendix B).

3.1.3 Evaluation of Concomitant Functional Digestive Disorders

Many patients with SOD III also have symptoms suggestive of other digestive motility disturbances, such as irritable bowel syndrome (IBS) (Evans et al., 1995; Desautels et al., 1999; Okolo P, et al, 1994; Linder et al., 2003). A key element of this study is to document these phenomena, and to assess whether or not their presence correlates with the findings of SOM, and/or predicts the outcome of treatment. The presence or absence (and severity) of other functional disorders (gastroduodenal disorders, bowel disorders, functional abdominal pain), will be assessed using the modular questionnaires updated recently by the Rome III committee (Behar et al, 2006; Drossman - see Appendix B).

3.1.4 Psychiatric Morbidity and Gastrointestinal Symptoms

There is increasing evidence for an association between psychiatric morbidity and digestive diseases. This association has been described primarily between psychiatric symptoms and gastrointestinal symptomatology, such depressive/anxiety symptoms and abdominal pain (Campo et al., 2003, 2004;Walker et al.,1992;Drossman et al., 2000;Bennett et al.,1998;Howell et al., 2003;Halder et al., 2002; Jones and Maganti, 2004; Koloski et al., 2002;Talley et al., 2001;Di Lorenzo et al., 2005). Less is known about the association between specific psychiatric disorders and digestive diseases (Mayer et al., 2001;Walker et al.,1990;Lydiard et al.1994). Even less data are available on the affect of psychiatric morbidity on the outcome of treatment in specific digestive disorders (Campo et al., 2004;Guthrie et al., 2004;Heymann-Monikes et al, 2000;Drossman et al., 2003).

Evaluating the presence of an association between SOD III and the occurrence and severity of psychiatric disorders of anxiety and depression is one of the secondary aims of this proposal. The reasons to suspect the presence of potential association are twofold. First, there are some data indicating the presence of high levels of depression and anxiety in patients diagnosed with SOD III, but their impact on response to treatment remains unknown (Desautels et al., 1999, Okolo P, et al, 1994). Second, data point to the presence of common biochemical mediators of key symptoms in both disorders. Specifically, serotonin (5-HT) and a variety of neuropeptides such as substance P, neuropeptide Y, and cholecystokinin have been implicated in the etiology of depression and anxiety and are key elements in the innervation of the sphincter of Oddi (Sand et al., 1994, Holmes et al., 2003, Blier et al., 2004, Hillsley and Mawe, 1998, Wunderlich et al., 2002). These data provide a rationale for the prospective evaluation of the presence and severity of anxiety and depressive disorders in the subjects of this trial.

Study results could identify a set of clinical variables that help to anticipate response to treatment. For example, if the presence of anxiety or depression predicts poor response to sphincterotomy, clinicians may choose to avoid this particular intervention, or may decide to treat co-morbid psychiatric disorders more aggressively before recommending endoscopic intervention. In contrast, if patients suffering from anxiety and depression demonstrate better response to sphincterotomy, this intervention may precede psychiatric treatment. These study results will be exploratory in nature, rather than providing definitive answers. However, the potential clinical relevance of these findings justifies the inclusion of psychiatric measures in the study.

3.1.5 Economics of SODIII

SOD III is a common and costly condition where an effective early treatment may be expected to improve patients' future QOL, and to reduce the cost of medical care for their remaining lifetime. The expected cost of SOD III includes inpatient care, medications, follow-up care necessary for the management of pain and associated problems, and possible indirect costs such as lost time from work. Given the significant financial burden that SOD III places on patients, providers, and payers, economic analyses should accompany trials that seek to improve outcomes for SOD III patients. Because "good value" should be demonstrated for any additional funds spent on new therapies, we must examine more than one economic parameter and compare treatment groups at more than one time to identify the economic benefits and/or burdens that should inform the discussion about the adoption of a new and costly therapy. In one of the only economic evaluations of patients with SOD, Arguedas, Liner and Wilcox (Co-Investigator) recently modeled the economic implications of empirical biliary sphincterotomy versus manometry-guided therapy in patients with suspected SOD II (2004). Their results revealed that empirical biliary sphincterotomy performed by experienced endoscopists appears to be cost-saving for the initial episode of care in comparison with a strategy based on results of SOM. The EPISOD economic analysis will evaluate the economic impact of endoscopic sphincterotomy in patients with SOD III. Comprehensive information will be gathered on resource utilization and patients' valuation of their QOL over 12 months for all patients in EPISOD. This will allow us to estimate expected differences in health care costs over the first year, and differences in patients' value of their QOL over 12

months. From these measures we will calculate incremental cost effectiveness ratios and cost increases/cost offsets due to the differences in therapy.

3.2 Supporting Clinical Data

3.2.1 Overview

Four IRB approved studies have been performed at MUSC and 3 of the other 5 participating centers to determine study feasibility in terms of recruitment, instrument implementation and reliability, and data collection. The following is a summary of the pilot studies conducted for this submission.

a) Patterns of pain and disability in SOD patients.
Study A. A retrospective chart review of 39 patients who had undergone treatment for SOD III at MUSC showed that 4 (10%) reported daily pain (and would not be included using the new Rome III criteria). The remaining 35 had abdominal pain episodes, with 4 (11%) of these patients having pain only on one day in the month prior to their initial clinic visit. Of the remaining 31, the average number of days with pain episodes during the month prior to their clinic visit was 10 (range: 2- 26 days per month), with an average severity score of 8 (range: 4-10).

Study B. The newly developed RAPID instrument was tested in an ongoing prospective study of SOD III patients to assess the feasibility and reliability (test-retest) of the instrument. A total of 50 SOD III patients were enrolled at MUSC and at 3 of the participating study centers. Potential subjects were recruited through the existing referral network at each participating center, and completed several questionairres administered by telephone at their first visit (baseline) and during a 3-month follow up period. These were the RAPID, RAPID Start (a 16-item tool designed to collect information regarding pain descriptors, gallbladder surgery, tests, treatment and/or the need for urgent medical care to address pain problems), and SF36. The pain episodes (questions 6-7 on RAPID) at baseline occurred at an average frequency of 70 pain days per 3-month interval (sd:29; range:3-90), with over 70% of subjects reporting a pain severity level of greater than 5 on a 10-point scale; 38% reported a severity level of 8 or greater. The RAPID score is interpreted according to the Grades used for the MIDAS scale (Lipton, 2001). In summary, the score is a 90-day summation of missed days and days where productivity for paid work or school, household activities and non-work activities are reduced by half due to abdominal pain episodes. Grade 1 is a score of 0-5 and indicates little or no disability. Grade 2 is a score of 6-10 and indicates mildly limiting disability. The RAPID scores for Grade 3 and 4 are 11-20 (moderately limiting disability) and 21 or greater (severely limiting disability), respectively. Pretreatment, 82% of the subjects had severely limiting disability (RAPID Grade 4). Figure 1 illustrates the percentage of subjects in each grade prior to treatment.

b) Reliability of the RAPID scores.
In Study B the RAPID instrument was telephone-administered twice at baseline (at 2-3 week intervals) in 24 subjects. A two to three week period is long enough

to minimize the effect of recall on test-retest reliability and short enough to minimize any effect of change in pain experience. The test-retest agreement was 0.80 (Lin's concordance coefficient, 1989).

Study C**.** In another retrospective study conducted at MUSC, 70 patients who had undergone a sphincterotomy completed the RAPID in order to assess the test-retest of the instrument and to document the range of disability in this patient population. The RAPID was administered twice by phone at 2-3 week intervals, 6-18 months post-sphincterotomy. The test-retest agreement for the RAPID was 0.95.

c) Treatment response.
Studies B and C used the RAPID instrument to assess the status of SOD III patients before and after (respectively) standard treatment (sphincterotomy). Figures 1 and 2 illustrate the pre- and post-sphincterotomy responses to treatment, respectively. Over 80% of the prospective study population was Grade 4 at baseline, whereas after treatment, nearly 60% of the comparable retrospective study population was Grade 1. Thirty-four percent were Grade 4. Although there are limitations to this type of comparison, it does illustrate that the RAPID appears responsive to treatment.

Figure 1: Pre-Treatment RAPID Grade (n=56)

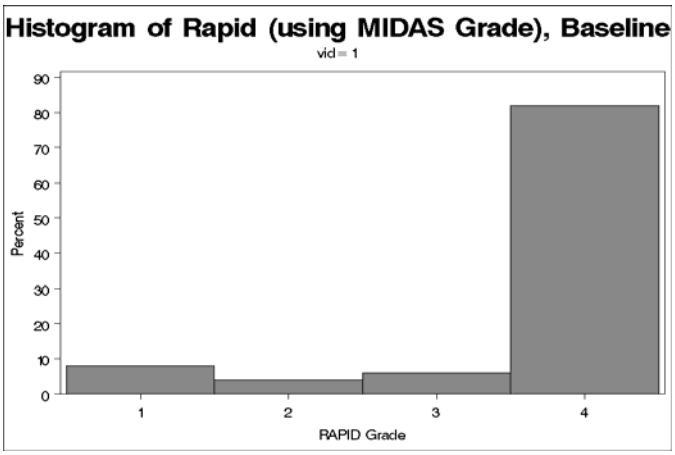
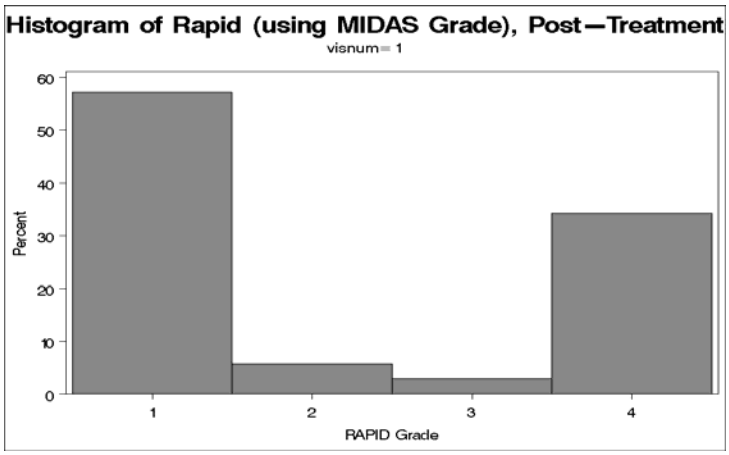


Figure 2: Post-Sphincterotomy RAPID Grade (n=70)



Study D. Outcomes in 35 patients who had undergone sphincterotomy for SOD were documented at MUSC and at Digestive Health Associates of Texas. Eligibility criteria included: ≥ 18 years of age, ERCP between January and December 2003 (with no prior ERCP) and a final diagnosis of "Papillary Stenosis/Spasm." By telephone follow-up, patients were asked to rate their status in regard to the sphincterotomy treatment, using the PGIC scale. Nine patients were very much improved, 11 were much improved, 8 minimally improved, 5 unchanged, 2 slightly worse, and none were much or very much worse. None of the assessed patients had undergone a 2nd intervention at the time of assessment.

The results of these pilot studies are good evidence that many patients with SOD III have severe disability which may be impacted positively by endoscopic sphincterotomy, and that the RAPID instrument is clinically logical, reliable, and sensitive to change.

3.3 Rationale

The rationale for a Phase III randomized sham-controlled trial of endoscopic sphincterotomy is the following:

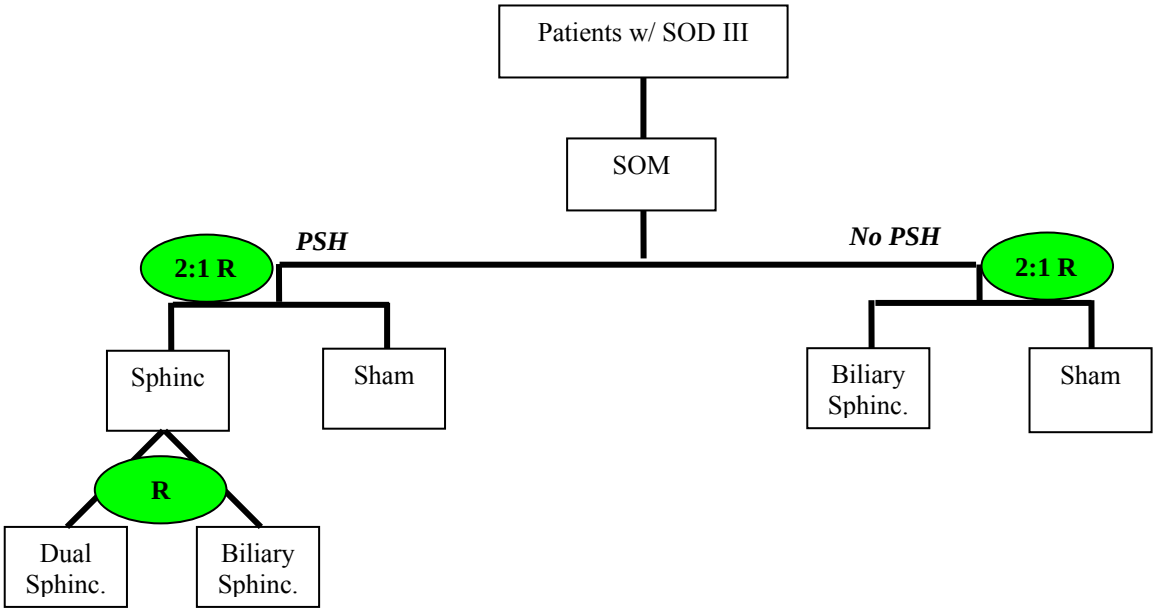
- The methods for recognition and treatment of SOD III are controversial and not without hazard (Steinberg, 1988; Petersen 2004[1], Petersen 2004[2]). The importance of further studies in this area was emphasized strongly in the report of the "State of the Science" conference on Endoscopic Retrograde Cholangio Pancreatography (ERCP), which was held by the National Institute of Health in January 2002 (Cohen et al., 2002; Sherman, 2002; Pasricha, 2002).
- SOM is widely used as the "gold standard" for diagnosis and exclusion of sphincter dysfunction (Hogan, et al., 1997; Corazziari et al., 1999; Sherman and Lehman, 2001; Viceconte and Micheletti, 1995). However, this belief is based largely on studies in patients with SOD Types I and II, and has not been established in Type III.
- More than 100 patients with suspected SOD III are referred to the Digestive Disease Center (DDC) at MUSC every year, and are currently treated according to the results of SOM. However, only about 70% of SOD III treated patients improve with this approach here and in other centers (Kalloo and Pasricha, 1996; Botoman et al., 1994; Wehrmann et al., 1996; Toouli et al., 2000; Petersen 2004[1], Petersen 2004[2]), indicating that SOM is not completely accurate in this context. Inadequate positive and negative predictive values of SOM have significant implications for patient management. In current practice, some patients undergo sphincterotomy with no benefit (and some risk), while others may be denied useful treatment. SOM is available in relatively few centers, and carries a significant risk of provoking pancreatitis (Sherman et al., 1991; Chen et al, 1994; Freeman et al., 1996; Maldonado et al., 1999; Freeman et al., 2001). Its continuing use requires validation.
- The financial implications of inappropriate management of SOD III patients can be significant. To date, no formal cost-effectiveness analysis regarding SOD III has ever been performed.

4.0 STUDY PLAN

4.1 Study Design

This is a multi-center, randomized, sham-controlled study designed to assess the overall value of endoscopic sphincterotomy as treatment for adults 18 to 65 years of age diagnosed with SOD III. A total of 214 subjects will be randomized using a 2:1 allocation in favor of sphincterotomy and will be followed for 12 months post-randomization according to the Data Collection Schedule (below). Subjects completing the 12-month follow up who indicate that they have minimal or no disability due to their abdominal pain episodes (RAPID Grade 1), at both months 9 and 12 post-randomization, are considered successes. All other subjects are considered failures including subjects who have been referred for further sphincter procedures during the year, or who have more taken any prescription analgesic use during months 10, 11 and 12 unless taken for non-abdominal pain, and then for less than 14 days in months 10,11 and 12. The primary reasons for choosing an unequal treatment allocation are the importance of acquiring as much information as possible on the effect of sphincterotomy in SOD III patients, and the anticipated difficulties of getting patients to accept randomization to a sham arm.

Refer to the below diagram of the randomization scheme. In addition, a careful follow-up study, EPISOD2, of standard of care treatment in patients who decline randomization will be performed (separate protocol).



4.2 Study Sites

The Medical University of South Carolina will act as the Clinical Coordinating Center for approximately 6 – 10 sites throughout the United States.

4.3 Estimated Study Duration

Initiation of Study	6 months
Subject Recruitment	36 months
Pre-Treatment/Treatment/Follow-up	12 months
Analysis and Reports	6 months
Total:	60 months

5.0 ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

1. Patients diagnosed with the clinical syndrome of SOD, as defined by the Modified Functional Biliary Disorders Module of the Rome III criteria.
2. Pain burden of Grade 3 or higher on RAPID Questionnaire.
3. Cholecystectomy more than 90 days before enrollment.
4. Laboratory Tests: Results of blood tests taken within 1 week preceding the baseline visit and any others available from the preceding 6 months (post-cholecystectomy):
   - Direct bilirubin, alkaline phosphatase, amylase and lipase results must no greater than 2 X upper level of normal (ULN)
   - Transaminase levels can be no more than 3 X upper limit of normal (ULN).

   Normal abdominal imaging by CT or MR/MRCP with bile duct reported at ≤ 9mm.
5. Upper endoscopy examination without findings to explain the pain.
6. Pain persisting despite a trial acid suppressant medications for one month (if tolerated)
7. Pain persisting despite a trial of PRN antispasmodics.
8. Subjects on antidepressants for pain control (not required) should be taking them for a minimum of one month prior to the baseline assessment.
9. Patients with SOD with depressive and/or anxiety disorders who receive psychopharmacologic treatment must be on stable medication dose for at least 6 weeks.
10. The total number of days in the previous 3 months that the subject has taken prescription analgesics due to episodes of abdominal pain is not greater than the total number of days the subject has episodes of pain.
11. Access to a telephone.
12. Able to speak, read, and write English.
13. Signed and dated informed consent.

5.2 Exclusion Criteria

Pre-ERCP Criteria:

1. Prior ERCP treatment.
2. Age < 18 or Age > 65.
3. Pregnancy: Women who are pregnant at the time of Screening* will be excluded from the study. (*Note: Women who become pregnant AFTER the Baseline Visit/ERCP will be allowed to remain in the study for telephone follow-up visits).

4. Prior gastric resection or surgery involving biliary diversion.
5. Prior diagnosis of acute pancreatitis (lipase >3 x ULN) including post-ERCP pancreatitis, or of chronic pancreatitis by radiological imaging, EUS 5 or more criteria, or Cambridge criteria moderate or more on ERCP.
6. Daily use of prescription analgesics over the previous month.
7. Presence of significant psychiatric disorders:
   a. Lifetime psychotic disorders, bipolar disorder;
   b. Substance use disorders within 6 months;
   c. Eating disorders within 2 years;
   d. Moderate & severe depression as defined by BDI-II cutoff scores (Beck Depression Inventory) total score $\geq$ 22, unless there is evidence of an appropriate assessment of their condition by a mental health professional who has to establish that the patient is being appropriately managed and is clinically stable; and/or,, Suicidal risk (equal to or greater than "low") using MINI suicide section or a score of greater than 0 on question 9 of the BDI.
9. Any condition that, in the investigator's opinion, makes the subject unsuitable for study participation.

ERCP Criteria:

1. Pancreas divisum (complete or partial) (known or discovered at study ERCP).
2. Any pathology found at ERCP (except sphincter hypertension).
3. Failed pancreatic manometry.

* *Justification for restricting age between 18 and 65:* SOD III occurs mainly in patients aged between 20 and 50. Patients over 65 are more likely to harbor other diseases (e.g. pancreatic tumors) that may present with similar symptoms, and are also more likely to have concomitant disabilities (some painful) that will affect their QOL and will confuse measurements of treatment benefit.

6.0 SUBJECT RECRUITMENT

6.1 Screening of Potential Subjects

The primary means for recruitment of subjects is to ensure rapid identification of potential study candidates at the respective centers and to minimize the time for evaluation and treatment. All patients currently receive a packet of materials to complete and bring to the clinic. This includes records of past illnesses, surgeries and evaluations, allergies, laboratory and radiological studies. After standard evaluation in the clinics, patients who have pain, and who may be categorized as suffering from SOD III will be interviewed by a research coordinator to establish eligibility criteria and obtain 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 18 through 65 years of age, with post-cholecystectomy pain and no previous ERCP treatment (i.e. sphincterotomy) who are screened for the EPISOD Study but not enrolled (regardless of whether or not he/she signed informed

consent) will be recorded on the EPISOD Screen Failure Log. A reason for exclusion for each patient not entered into the trial will be recorded.
Further details on the completion of the Screen Failure Log are located in the EPISOD MoP.

7.0 SUBJECT ENROLLMENT

7.1 Pre-Randomization Eligibility Assessment

The designated centers all have specialized pancreatico-biliary clinics which receive patients through their existing referral networks and scheduling offices. Patients undergo standard clinic evaluation, with any additional clinically indicated tests (e.g. laboratory studies and scans). If ERCP (with SOM and sphincterotomy if indicated) is recommended, it will be scheduled usually on the following day. Patients will complete the standard medical consent for ERCP at each center. Patients with symptoms suggestive of SOD III will be interviewed by a study coordinator at the site to assess preliminary eligibility, explain the study and conduct the research informed consent process. All centers will use an IRB-approved script for screening patients similar to the script used in the pilot projects. Once the subject agrees to participate in the study and signs the consent, baseline data will be aggregated from the clinical data already collected and subjects will be asked to complete a series of instruments as detailed below.

As in all trials, the goal is to achieve a high level of compliance with protocol requirements by assuring, during the eligibility assessment that the potential subject is fully informed and agrees to the protocol requirements. In addition, subjects with a strong likelihood of non-compliance should not knowingly be registered. Adherence of the clinical center staff to careful assessment of the subject's understanding of the trial and a clinical center environment which supports the continued commitment of the subjects are essential for the trial to be successfully completed.

Eligibility assessment will include:

1) Verification that 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, and copies of all pertinent reports (*e.g.,* pathology and laboratory) have been obtained;

5) Signed and dated informed consent.

7.2 Presentation of Informed Consent

All centers will use an IRB-approved consent document similar to the consents used in the pilot projects. 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 Coordinating Center. The initial consent will be the most recent IRB-approved version.

Informed consent will be obtained from subjects prior to the initiation of any pre-trial procedures that would not have been performed 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.

7.3 Subject Enrollment and Randomization Procedures

Specific details on Enrollment and Randomization Procedures are outlined in the current version of the MoP located on WebDCU™. Clinical Centers should refer to the MoP for these procedures. Below is a summary of procedures.

Enrollment: At each Clinical Center, the Enrollment procedure is as follows:

(1) Each Clinical Center will have **designated staff** who will perform enrollment procedures.

(2) **Designated staff** will log onto the study specific Enrollment website and enter the required information into the computer system on a data entry screen. NOTE: If, under rare circumstances the web system is not available, the coordinator will have a contact number for Data Coordination Unit (DCU) staff who can manually perform the enrollment process.

(3) The computer will assign a unique subject ID number which will appear on the computer screen. This will be the subject's unique identifier throughout the study. Designated staff will print the

computer screen and file all enrollment information in the study specific files.

Randomization: Randomization will be conducted centrally using the WebDCU™ system.
At each Clinical Center, the Randomization procedure is as follows:

(1) Each Clinical Center will have **designated (unblinded) staff** (not the study coordinator conducting the follow up assessments) who will perform randomization procedures at the time of ERCP and communicate the assigned treatment arm to the treating (unblinded) physician.

(2) Inclusion and Exclusion criteria Form 01 must be entered, and submitted into the WebDCU electronic case report form, by a site coordinator. The source document for Form 01 must be verified and signed by a site investigator before randomization can occur. If this form is not submitted and all eligibility criteria met, randomization will be blocked by WebDCU.

(3) **The Designated (unblinded) staff**, will log onto the study specific Randomization website and enter the required information into the computer system on a data entry screen. NOTE: If, under rare circumstances the web system is not available, the coordinator will have a manual randomization process as outlined in the EPISOD MoP.

(4) The cohort (PSH/non-PSH) and treatment assignment of each subject is confidential and should not be shared with anyone but the treating physician. Designated (unblinded) staff will print the computer screen and file all unblinded randomization information separately from the other study specific files.

8.0 STUDY PROCEDURES

8.1 Screening/Baseline Visit (Initial Eligibility)

The following events will occur during the Baseline Screening visit. All screening tests and evaluations used to determine the initial eligibility of participants will be assessed and documented.

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. However, the informed consent form must be obtained and documented in the

subject record prior to initiation of any study procedures performed solely for the purpose of determining eligibility for research. A copy of the signed and dated consent form will be given to the subject and the original consent document will be filed in the subject record.

8.1.2 Medical History & Record Review: Medical history will include questions about current medications, previous medical or emotional history and psychiatric history or treatment. All ALLERGIES will be reviewed and recorded and all concomitant medications will be reviewed and documented including prescription medications, over-the-counter medications (i.e., Tums, cough syrup, vitamins and minerals, etc.), herbal preparations (i.e., St. John's Wort, ginkgo biloba, ginseng, Melatonex, etc.), and nutritional supplements (i.e., Ensure, power bars, etc. Results and reports from laboratory tests and/or other procedures will also be reviewed and documented to ensure eligibility with inclusion/exclusion criteria. All labs taken within 6 months of study enrollment must meet eligibility requirements in order for the subject to be eligible for randomization.

8.1.3 Interviews & Surveys: An initial interview (MINI) and additional assessment instruments (outlined in Section 8.8) will be administered as part of the Baseline Visit. To ensure confidentiality of sensitive information, the Trauma Scale and Coping Strategies questionnaires will be placed in a sealed envelope as soon as completed by each subject to be reviewed and scored by a the study coordinator at a later time. In addition, the MINI will be videotaped for two subjects per site per year for quality assurance purposes.

8.1.4 Physical Examination: Subjects will receive a general physical examination including vital signs, assessment of the head and neck, abdomen, extremities and examination of the heart and lungs.

8.1.5 Laboratory Tests

Blood Tests: If the potential candidate has results from previous laboratory tests (dated within the last 6 months), those tests should be provided to the treating physician for screening purposes. Labs must be drawn within 1 week of study enrollment. Blood samples will be obtained including a complete blood count (CBC), liver function tests (LFTs) and Amylase/Lipase tests. All labs taken within 6 months of study enrollment must meet eligibility requirements in order for the subject to be eligible for randomization.

- **Pregnancy Test:** Women who can possibly be pregnant at the time of Screening* will have a blood serum pregnancy test performed. Upon a positive HCG result the subject would be excluded from enrollment in the EPISOD trial. (*Note: Women who become pregnant AFTER the Baseline Visit/ERCP will be allowed to remain in the study for telephone follow-up visits).

H. Pylori Test: Documentation of previous test results or eradication therapy will be collected, but not used in inclusion or exclusion of potential candidates.

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List of Screening & Evaluation Procedures
• Informed Consent • Review of Medical History & Current Medications • Results of previous Laboratory Tests, Imaging Results • Physical Examination, laboratory tests, vitals. • MINI Interview • Questionnaires: RAPID, BDI-II, HADS, TRA, CSQ, Rome III Modified Functional Biliary Disorder Module, RAPID Start, SF-36, ROME III Diagnostic Module, and Resource Utilization Questionnaire

8.2 Endoscopic Retrograde Cholangiopancreatography (ERCP)

8.2.1 Investigator Training

Although ERCP, sphincterotomy and the interpretation of SOM are standard of care procedures routinely performed by participating gastroenterologists, a mandatory training session will be conducted at the initial EPISOD Investigator Meeting for all procedures, methods and techniques performed as part of this study. Investigator training is designed to ensure standardization and consistency between participating centers for all procedures performed as part of the EPISOD trial. Additional training sessions will also be conducted at annual meetings throughout the study.

8.2.2 ERCP & Follow Up

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

EPISOD: ERCP & Randomization
• Standard Procedure Consent • ERCP • SOM • Randomization • Stent • *Sphincterotomy** • Recovery • 24 hour hospitalization for observation • Amylase and Lipase Labs • Discharge (with Research Packet)

Sphincterotomy only performed on subjects randomized to that treatment arm.

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:** Most patients 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 (ie, Metformin (glucophage) to control diabetes, insulin, Anticoagulants such as Coumadin, nonsteroidal anti-inflammatory drugs (NSAIDs), Antacids and Aspirin). If approved by the physician, a small amount of liquid may be allowed to swallow important medications.

- **ERCP Procedure:** The ERCP procedure takes 30 - 90 minutes. Prior to the procedure, subjects will be placed on the left side on an examining table followed by administration of sedation or anesthesia. The endoscope will be guided through the esophagus, stomach, and duodenum until it reaches the point where the ducts of the biliary tree and pancreas open into the duodenum. Subjects will then be turned to lie flat on their stomach as the physician passes a small catheter through the scope and injects fluoroscopic dye into the ducts. X rays will be taken as soon as the dye is injected. Gallstones, narrowing of the ducts, pancreas divisum or other pathology(ies) may be revealed during examination and can be treated or resolved during this part of the procedure and/or biopsies can also be taken for further testing.

  NOTE: SUBJECTS IDENTIFIED AS INELIGIBLE DURING THIS PORTION OF THE ERCP WILL *NOT BE RANDOMIZED*.

  - An End of Study form will be completed for each enrolled subject that is not randomized.
  - Enrolled 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.

  If no structural pathology is found, and if pancreatic manometry is successful, randomization will be performed by the designated (unblinded) staff in the endoscopy suite at each site. The subject is considered to be

randomized when the treatment is assigned and will be followed and included in the primary outcome analysis, regardless of whether or not the subject receives the assigned treatment.

All randomized subjects will receive a small temporary pancreatic stent at the time of ERCP (unless pancreatic duct anatomy is deemed unsuitable by the treating physician). These stents are designed to pass spontaneously in about 2 weeks, and are standard clinical practice to reduce the significant risk of post-ERCP pancreatitis in such patients. The temporary stent is not considered to be a treatment for SOD III. About 10% of these stents fail to pass within 4 weeks but are easily removed through a simple upper endoscopy procedure.

The results of the ERCP (and SOM) and the therapy performed will be maintained in the EPISOD research record for each subject (not the medical record) to ensure continued blinding.

8.3 Manometry

Sphincter of Oddi manometry will be performed in the standard manner during the ERCP procedure, with attention to details of medications, techniques and interpretation, as outlined below, agreed at a meeting of investigators. If the pancreatic manometry cannot be performed then the subject is considered ineligible for randomization and the End of Study form should be completed. The randomization process should not occur.

8.3.1 Medications immediately before and during SOM

All are acceptable, including general anesthesia, except high-dose prescription analgesics (i.e. > 1 mg/kg Meperidine, >1 mcg/kg Fentanyl), anti-cholinergics, smooth muscle relaxants and Glucagon.

8.3.2 Technique

5 Fr Triple-Lumen aspirating catheter. Perfusion: 0.25 ml/channel/min via low-compliance pump. If a guide wire is necessary to achieve deep cannulation, pull the wire back into the catheter (out of the duct) for SOM. One pull through is sufficient if tracing quality is good; repeat pull-through if suboptimal.

8.3.3 Interpretation

SOD (biliary and pancreatic) are defined by a Basal sphincter pressure (BSP) $\geq$ 40 mmHg, sustained for 30s in <u>BOTH</u> leads, with final BSP = mean of lead 1 + 3. Each pressure will be the average of the 4 lowest amplitude points within the high pressure zone with no measurement being < 40 mmHG. Phasic wave characteristics will be evaluated but <u>not</u> used to define SOD.

8.4 Sphincterotomy

If assigned by randomization, biliary and/or pancreatic sphincterotomies will be performed in the standard manner, using pull-type and/or needle knife devices.

8.5 Sham

Subjects allocated to sham treatment will have a pancreatic duct stent placed (as in all other subjects) after the manometry procedure, but no sphincterotomy. Stents will not be placed in a few patients if pancreatic duct anatomy is deemed unsuitable by the treating physician.

8.6 Follow-Up Assessments

8.6.1 Immediate Post-Procedure, Observation and Discharge

Subjects will be observed in recovery and admitted overnight in hospital for 24 hour observation. The subject will be interviewed the next morning by the treating physician and research coordinator, and blood drawn for amylase and lipase. In the centers where such patients are usually discharged a few hours after the procedure (if stable), the subject should be seen next day by the treating physician and research coordinator, and blood drawn for amylase and lipase. At discharge, all subjects will be given standardized safety instructions, contact information and recommendations for clinical follow-up. Depending on local practice, and the distances involved, further clinical care will be rendered by clinicians at the treating center, or by the referring physician. Further clinical care will be documented during the follow up phone calls.

Prior to discharge, subjects will receive a study packet containing a copy of the EPISOD consent, a 12-month subject-specific calendar outlining the planned telephone follow-up to be conducted by the study coordinator, copies of required questionnaires for future reference during the scheduled telephone calls and emergency contact information for the EPISOD trial. Further clinical care will be provided as clinically indicated for each individual subject by clinicians at participating sites or referring primary care physicians in accordance with local clinical practice standards and institutional policies.

8.6.2 Temporary Stents

Temporary stents are designed to pass out of the pancreas and out of the body through the intestine after 2-3 weeks. Clinical follow-up (ie, x-rays) are performed by the referring physician (primary internist or gastroenterologist) at 3-4 weeks to check that the stent is gone. About 10% of these stents fail to pass in 4 weeks, and must then be removed by a simple upper endoscopy procedure. Subjects who require an upper endoscopy for removal of the stent may return to

the research facility or to the referring physician for this procedure. This procedure should be recorded on the concomitant treatment case report form.

8.6.3 Post-Intervention Evaluations

Subjects are followed for 1 year from randomization. Follow-up efficacy data will be collected by telephone at 1 week, 1 month and 3 months post-randomization and every 3 months thereafter for a total of 12 months. Follow-up safety data will be collected by telephone monthly (starting 1 month post-sphincterotomy) for adverse events and medication use. Since most subjects live a significant distance from the centers, follow-up of subjects will be conducted by telephone (by study coordinators) rather than clinic visit. Subjects will be asked questions from required instruments (RAPID, BDI-II, HADS, SF-36, MAPA, & Follow Up Resource Utilization) over the phone using a copy of questionnaires provided at discharge for reference during the call. The study investigator or their staff will respond to any subjects presenting suicidal ideations by using standard psychiatric procedures for safety purposes. Laboratory tests will be performed as clinically needed throughout the study, and subjects will return to the center for repeat evaluation if and when they or their referring physician requests.

At the 1 week, 3 month, 6 month, 9 month, and 12 month visit, the subject and interviewing study coordinator will complete a 'Best Guess' questionnaire. These assessments ask the person completing the form to guess which treatment to which the subject was randomized. These forms allow for assessing the quality of the blind at each clinical site.

Visit Windows: The timeline of telephone 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 telephone assessments will occur at +/- a certain number of days. The study data should always be collected regardless of its tardiness.Proposed time windows are available in the MOP. Three attempts should be made when contacting subjects by telephone followed by one certified letter if the telephone attempts have failed. The coordinator may ask the treating physician to make an attempt to reach the subject. Beyond this, the site can determine if they would like to make further attempts.

Central Caller: The RAPID assessment will be collected at Months 9 and 12 by a central caller housed at the Clinical Coordinating Center. This procedure is in place to maintain the treatment blind for the primary outcome. At Months 9 and 12 the central caller will telephone the subject to administer the RAPID. The sites will not have to administer this instrument during months 9 and 12 follow up calls.

8.6.4 Final Evaluations

At the 1-year anniversary date of each subject's randomization date, the study coordinator, or other designated (blinded) personnel will contact the subject via

telephone to review AEs and concomitant medications/interventions since the last contact, to conduct final instrument assessments (SF-36, Follow Up Resource Utilization, HADS, BDI- II, HADS) and to complete the end-of-study CRF. The final (12-month) RAPID will be administered by a central caller as described above.

All subjects are followed using the intent-to-treat principle. Thus, regardless of whether or not a subject has completed the primary endpoint assessment, all follow-up procedures will be performed according to the standard schedule.

8.6.5 Subject Compensation

Subjects will be compensated for completing telephone visits at months 6, 9, and 12 (to include central caller visits) if those visits are completed within the prescribed visit window. The compensation will consist of a $50.00 stipend for each completed telephone visits defined in this section.

9.0 REINTERVENTION

Subjects who report inadequate improvement or worsening in SOD-related disability and/or who develop significant new abdominal symptoms can request a review appointment with an 'evaluating physician' (EP) at the research site (regardless of randomized treatment assignment).

9.1 Evaluating Physician (EP) Evaluation: To reduce variability in criteria for considering re-intervention, each participating site will identify a sub-investigator "evaluating physician" (EP) who is blind to the subject's randomized treatment. The EP will complete a 'Best Guess' questionnaire at all unscheduled visits to assess the quality of the blind.

To ensure standardization, the EPs will receive equal and intensive investigator training regarding the EPISOD protocol prior to start-up and enrollment.

- **The designated EP at each site will assess the subject's clinical progress by standard enquiry, physical examination and laboratory tests if clinically indicated, and will have access to the RAPID scores.**
- Follow-up safety data will be collected including a review of concomitant medications and/or treatments (post-baseline). Adverse events will be reported and documented in accordance with the protocol and local institutional requirements.
- **The EP will recommend either: (1) continuation of conservative therapy (surveillance); or, (2) referral for consideration of further sphincter evaluation and treatment (endoscopic or surgical).**
- **Once the EP has reviewed the information provided by lab tests, questionnaires, etc, and make their determination as to a recommendation for either continued surveillance or further treatment, the subject is then returned to the TP (treating physician)**

for all clinical care. The role of the EP is strictly that of a reviewer for the study.

Guidelines for referral for consideration of further sphincter evaluation and treatment: In general, subjects will not be referred for consideration of further sphincter evaluation and treatment **if the RAPID score has fallen >50% from baseline**.

Subjects who are referred by the EP for consideration of further sphincter evaluation will be deemed a failure in terms of the primary outcome (even if there is no re-intervention). Data concerning secondary objectives will continue to be collected for 12 months post-randomization. Subjects and study coordinators should remain blinded to the initial randomization treatment until the end of the study.

All standard medical care will be provided to subjects who fail the primary outcome.

10.0 DATA COLLECTION INSTRUMENTS

10.1 Assessment Instruments

The following instruments will be administered:

10.1.1 The Mini International Neuropsychiatric Interview (MINI): (Sheehan et al., 1998). This is a validated structured psychiatric diagnostic interview, which allows for the determination of the presence or absence of psychiatric diagnoses, both lifetime and current. This instrument has been extensively used in multicenter clinical trials and epidemiologic studies and in outcome tracking in non-research clinical settings.

10.1.2 Recurrent Abdominal Pain Interference and Disability (RAPID): This instrument models the validated migraine scale, MIDAS, and measures the days lost in social, household work/chores and employment due to episodes of abdominal pain on a 3-month recall basis.

10.1.3 Beck Depression Inventory (BDI-II): (Beck et al., 1996). This is a validated 21 item self-report rating inventory measuring characteristic attitudes and symptoms of depression. BDI is one of the most widely used instruments for measuring the severity of depression. The BDI takes approximately 10 minutes to complete, and requires a fifth – sixth grade reading age to adequately understand the questions.

10.1.4 Rome III Modified Functional Biliary Disorder Module (FBDM): The FBDM is one of several modules contained in the Rome III diagnostic questionnaire which is generally designed to identify a variety of functional gastrointestinal disorders. Since the FBDM focuses specifically on gallbladder and Sphincter of Oddi disorders, it can be used to confirm whether the subject has the clinical syndrome of SOD as defined by Rome III Criteria, hence will be administered PRIOR to the remaining Rome III modules (described in Section 10.1.8 below). The FBDM has been modified to allow discomfort on a daily basis. The FBDM will be completed by the subject and takes about 10 minutes to complete. **NOTE: Subjects who do not*

meet Rome III entry criteria as determined by the FBDM will not have to complete Rome III diagnostic modules.

10.1.5 Hospital Anxiety and Depression Scale (HADS): (Zigmond et al., 1983). This is a validated self-rating 14 item scale developed to assess anxiety and depressive symptoms, and various non-somatic anxiety and depressive symptoms. HADS is sensitive to changes both during the course of diseases and in response to therapeutic interventions. HADS has been routinely utilized in clinical research trials in patients diagnosed with depressive and anxiety disorders.

10.1.6 Trauma Questionnaire – Short Form (TRA): Trauma Questionnaire – Short Form (TRA): (Leserman et al., 1996, 1997, Drossman et al., 1999) The TRA is a validated screening instrument developed to identify sexual and physical abuse in a medical population. Studies utilizing TRA indicate that patients with functional gastrointestinal disorders have a higher frequency of severe types of abuse than patients with organic GI diagnoses. Abuse history also significantly contributed to greater pain severity, more days in bed, more psychological distress, and poorer daily function in subjects with functional GI disorders.

10.1.7 Coping Questionnaire-Catastrophizing Subscale (CSQ-Catastrophizing): (Keefe et al., 1990; Drossman et al., 1999). This validated self-rated scale focuses primarily on cognitive coping strategies in response to painful conditions. The catastrophizing subscale includes negative self-statements and thoughts about the future in which the patient unrealistically assumes that the worst possible outcome will occur. High scores on this subscale, reflecting maladaptive coping, were shown to adversely affect health outcome and may modify the effect of gastrointestinal (GI) disease type on health outcome.

10.1.8 Rome III Diagnostic Module Functional Gastrointestinal Disorders: The updated Rome III modular questionnaire elicits responses that allow subjects to be categorized as having (or not) the major classes of functional disorders, (i.e. gastrointestinal, functional abdominal pain, biliary disorders, and bowel disorders). The purpose of this survey is to learn more about the health problems that people sometimes have with their stomach and intestines. As noted above, the Biliary Module will be administered PRIOR to the remaining Rome III modules. The questionnaire will be completed by the subject and will take about 15 minutes to complete.

10.1.9 SF-36: (Ware, 1987; www.sf-36.org/tools). The SF-36 is a comprehensive Quality Of Life (QOL) assessment tool that incorporates the major domains of QOL: physical functioning, emotional or psychological well-being, social functioning, and role functioning. The SF-36 is designed for use in evaluative studies and policy research, and has been recommended for use by the US Public Health Service's Panel on Cost-Effectiveness in Health and Medicine (Gold et al, 1996).

10.1.10 Economic Resource Utilization Forms (RUF): For this study, the cost of the *initial hospitalization* of patients randomized to endoscopic sphincterotomy will be estimated by collecting UB-04 hospital billing forms for each initial hospitalization. This is a uniform billing statement used by all third party carriers. Charges are available for, but not limited to, endoscopy suite, post-procedural floor

care, anesthesia, recovery room, medical and surgical supplies, laboratory costs, pharmaceutical costs, telemetry and social services. Follow-up resource utilization data in the form of answers to survey questions will be collected on separate telephone-administered case report forms (CRFs). The Baseline Resource Utilization Form and the Follow-up Resource Utilization Form (3 month recall) are one and two pages respectively, and capture information on hospitalizations, physician/professional visits, employment information, and personal patient costs.

10.1.10 RAPID START: This internally developed instrument documents key elements of the patient's pain history at the first consultation.

10.1.11 Best Guess Questionnaire: The Best Guess Questionnaires are instruments developed for the EPISOD study to assess the quality of the blind. This assessment will be completed by the subject, the interviewing study coordinator, and the evaluating physician through the course of the study to ensure that all appropriate parties remain blinded to the subject's randomization assignment.

10.1.12 Psychiatric Rating Integrity. Following initial training of all centers' approved raters, who will be administering the Mini International Neuropsychiatric Interviews, raters will videotape the screening diagnostic evaluation of the first eligible subject enrolled at each participating site. These videotapes will be reviewed by Dr. Brawman-Mintzer (Co-Investigator) or designee to assure appropriate administration of the instrument. Deviations or problems will be addressed in conference call supervision sessions with Dr. Brawman-Mintzer and/or designee.

Further, a total of two interviews per year (for the duration of study recruitment period) will be videotaped for each rater who is performing the diagnostic evaluations. These videotapes will be reviewed by Dr. Brawman-Mintzer (Co-Investigator) or designee to assure diagnostic consistency during the conduct of the study to prevent rating drift. Deviations or problems will be addressed in conference call supervision sessions with Dr. Brawman-Mintzer and/or designee.

10.1.13 Monthly Abdominal Pain Assessment (MAPA): This questionnaire helps determine the frequency and level of abdominal pain the subject has encountered over the previous 30 days.

11.0 CONCOMITANT OR ANCILLARY THERAPY

Throughout the study, concomitant medications or treatments necessary to provide adequate supportive care may be prescribed Also refer to Section 8.3.1 for prohibited medication for the manometry procedure.

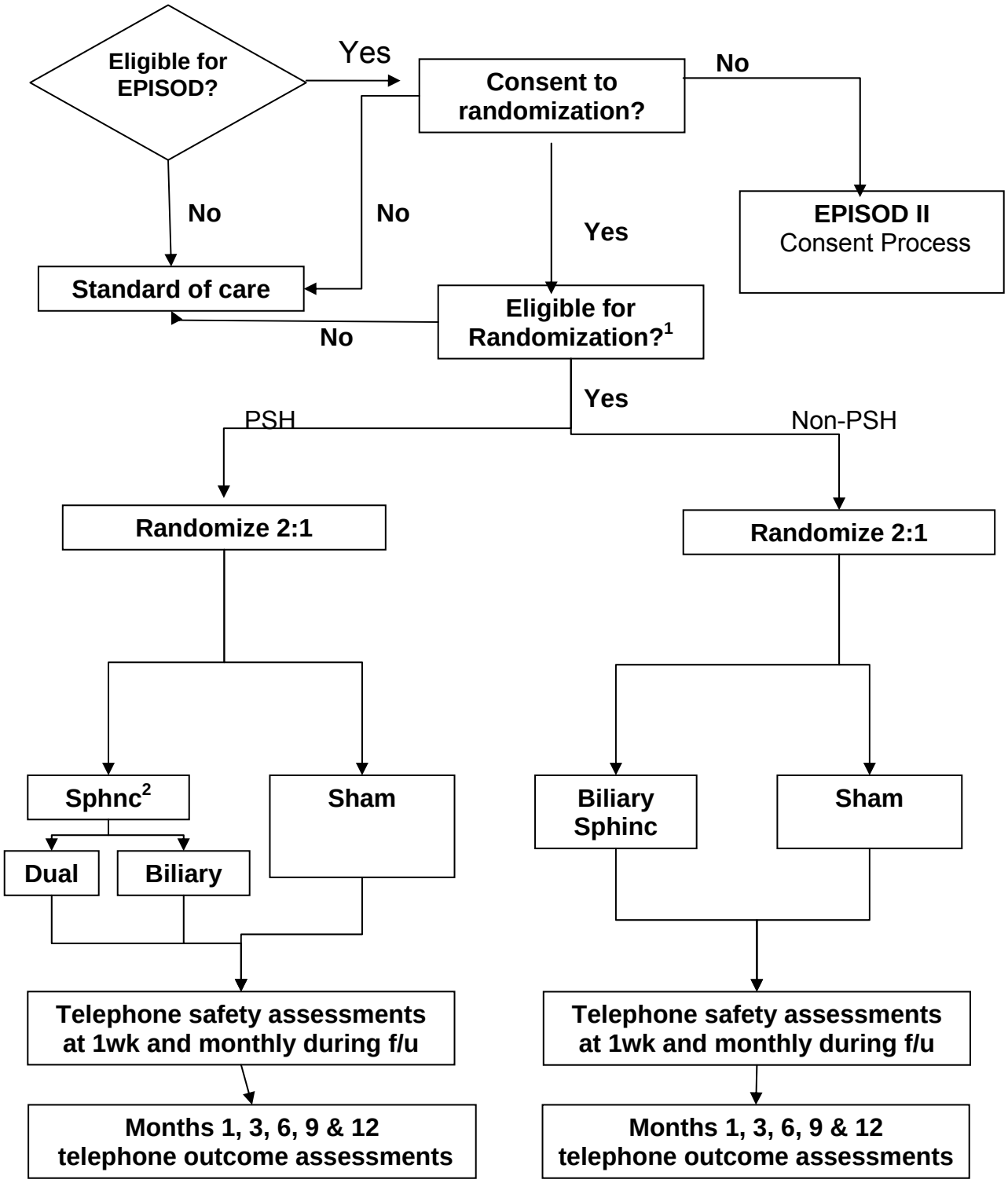
12.0 PROCEDURE FOR UNBLINDING

The Medical Monitor, Evaluating Physician, Subject and Research Coordinator conducting the follow up assessments are blind 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 personally must report the incident within one (1) calendar day of the unblinding to the EPISOD Project Manager, who will maintain a log of these unblinding events. 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 EPISOD MoP for emergency unblinding procedures.

13.0 STUDY FLOW CHART



[1] All eligibility criteria met including findings on the ERCP and SOM
[2] Second Randomization – done automatically by WebDCU™

14.0 DISCONTINUATION OF PARTICIPATION

14.1 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.

14.2 Subject Referred for a Re-intervention

Subjects who are referred by the evaluating physician for a reintervention will continue protocol-specified evaluations through the 12-month follow-up period unless they withdraw their consent to participate in the study. Standard clinical procedures may continue under the discretion of the primary physician.

14.3 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) A procedural complication, which would interfere with the subject's continued participation.

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

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

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

14.4 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.

14.5 Subject Lost to Follow-Up

All attempts to make contact with the subject will be documented in the study database. At a minimum, three attempts should be made when contacting subjects by telephone. If the telephone attempts have failed for the 12 month visit, a certified letter should be sent to the subject**.** When all possible attempts to locate the subject have failed, that subject will be considered 'lost to follow up'.

14.6 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 not be re-entered.

14.7 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.

15.0 OUTCOMES DEFINITIONS

15.1 Primary

It is hypothesized that among persons clinically diagnosed with SOD III, endoscopic sphincterotomy will result in a higher success rate than the sham intervention. Success is defined as subjects having a Grade 1 disability as measured using the RAPID scale at months 9 and 12 post-randomization, with no referral for possible re-intervention during the follow up period and who taken any prescription analgesic use during months 10, 11 and 12 unless the prescription analgesic is prescribed for pain other than abdominal pain and then no more than 14 days in months 10, 11, and 12. The relevant clinical outcome measure for success is to show that SOD III patients receiving endoscopic

sphincterotomy have at least a 30% higher success rate at a 12-month period than SOD III patients receiving sham (success $rate_{sham}$=30%; success $rate_{sphc}$=60%).

15.2 Secondary

This study is designed to test the primary hypothesis. However, it also offers the opportunity to conduct analyses to evaluate the diagnostic use of SOM, the pattern of episodic pain events in this sample as well as the association between these pain episodes and depression/anxiety.

15.2.1 Secondary Aim 1: In addition to testing the primary hypothesis, it is of clinical importance to evaluate the association between SOM results and the treatment outcome (Secondary Aim 1).

15.2.2 Secondary Aim 2: Also of clinical importance is to evaluate and compare the success rates of biliary and dual sphincterotomies (Secondary Aim 2). The subgroup (n~64) of subjects that has elevated sphincter pressures (PSH) and is randomized to either biliary or dual sphincterotomy will be evaluated.

15.2.3 Secondary Aim 3: To address Secondary Aim 3, evaluating the effects of pre-specified prognostic factors on the primary outcome, a logistic regression model similar to the primary model will be developed using the dichotomous primary outcome, treatment success/failure. The following covariates will be examined: baseline anxiety and depression levels (HADS/BDI), baseline psychiatric diagnosis (MINI), age, gender, BMI, and presence/absence of functional digestive disorders.

15.2.4 Secondary Aim 4: Since both SOD III and anxiety/depressive symptoms may be influenced by common neurochemical mediators, the change over time in depression and anxiety levels will be modeled using the follow up HADS scores.

15.2.5 Secondary Aim 5: The aim of the EPISOD Economic Study is to compare differences in medical resource use, cost effectiveness, and overall cost for the treatment approaches.

16.0 DATA MANAGEMENT

16.1 Site Monitoring

The designated monitor(s) will visit the Clinical Centers at specified intervals for the purposes of comparing source documents (such as hospital/clinical charts) to electronic 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 the 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.

16.2 Data Processing

The Data Coordination Unit (DCU) housed in the Department of Biostatistics, Bioinformatics and Epidemiology at MUSC will be the Statistical and Data Management Center (SDMC) for this trial and will handle data management and statistical analyses. The DCU has established a steadfast infrastructure for web-based data capture and data sharing, including designated web servers and supporting database servers. User-friendly web-based database systems have been developed, validated and used by DCU and clinical centers for on-line subject registration, data entry, data validation, project progress monitoring, user customizable report generation, lab specimen tracking, and secure data transfer. The web-based data capturing system allows for study data to be directly entered into the database via a secure internet connection. Secure Socket Layer (SSL) is used for data encryption. The web system combines all study tools into one system which includes study database, subject calendar, electronic data clarification request (DCR) process, case report form (CRF) and participate tracking system, audit trail, and report generation mechanisms. These reporting mechanisms are useful for study specific safety reports as well as study metrics including subject enrollment reports, data timeliness reports and data quality reports. The reporting mechanism allows authorized users to access real-time data that has been entered into the system and validated (via computerized rule checks). Authorized users can retrieve enrollment status, basic demographics and data summaries such as number of visits completed, number of resolved queries and outstanding queries. In addition to the password protected study data collection website (WebDCU™), the SDMC and CCC will develop a public access informational website available to the community to obtain information on participating sites, new research efforts in SOD and information for potential study subjects. For security reasons, this site will be separate from the WebDCU™ password protected data collection website.

16.3 Data Security and Confidentiality

During the course of the trial, user access to the files with Subject identifiers, treatment assignments, and files with study outcomes will be restricted to core staff with any exceptions to be approved by the Steering 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 without specific written instruction from the Steering Committee.

17.0 STATISTICAL CONSIDERATIONS

17.1 Sample Size and Power Estimation

The primary outcome variable is the overall proportion of subjects experiencing a successful procedure. Success is defined as subjects having a Grade 1 disability as measured using the RAPID scale at months 9 and 12 post-randomization, with no referral for possible re-intervention during the follow up period and who has taken

any prescription analgesic use during months 10, 11 and 12 unless the prescription analgesic is prescribed for pain other than abdominal pain and then for no more than 14 days in months 10, 11, and 12. Fifty-seven percent of the subjects in the retrospective pilot study (Study C) reached the RAPID criterion for success. This is consistent with Sherman and Lehman's extensive review that showed that approximately 60% of SOD patients have relief of pain (i.e., defined as not requiring re-intervention) after a sphincterotomy (Sherman & Lehman, 2001). Clinical experience and controlled studies with sham arms have estimated that 70% of SOD III patients who receive the sham intervention will return within 12 months of the procedure with the same episodes of pain (Geenen et al., 1989; Toouli et al., 2000; Petersen 2004[1]; Petersen 2004[2]).

A clinically relevant absolute difference in success rates between the two interventions (sham versus sphincterotomy) is chosen as 30% (success $rate_{sham}$=30%; success $rate_{sphc}$=60%). If the endoscopic sphincterotomy group does not have at least a 30% or higher proportion of successes than the sham group, then endoscopic sphincterotomy will not be considered a worthwhile therapy for SOD III patients (due to the known complication rate of the procedure).

Based on the above information and taking into consideration the planned interim analysis (as described below), the study is powered to assure greater than 90% likelihood of identifying a difference in success rates greater than or equal to 30%. Sample size estimation is based on the comparison of independent proportions with a 2:1 (sphincterotomy:sham) randomization scheme. This approach to calculating sample size is conservative. However, we expect to have at least 90% power to detect the estimated clinically relevant difference as logistic regression analysis (adjusting for strata) is generally more powerful than chi-square tests on individual outcomes. In addition, this sample size allows us to evaluate our secondary outcomes with adequate power (described below). The maximum sample size required for randomization is 192 subjects (128 in treatment and 64 in sham group). Assuming a 10% drop-out or lost to follow up rate, a total of 214 subjects will need to be randomized. This number is increased to 250 due to the anticipated 5% prevalence rate for pancreas divisum in this study population and roughly a 10% pancreatic SOM failure rate (both exclusion criteria) which will be determined at ERCP. Thus a total of 250 SOD III patients will be enrolled into the study and undergo an ERCP in order to reach the 214 that need to be randomized.

17.2 Other Statistical Considerations

17.2.1 Randomization Scheme

All enrolled subjects who meet the ERCP eligibility criteria will be randomized in a 2:1 fashion to sham or sphincterotomy. Randomization will be stratified by the presence or absence of pancreatic hypertension

(PSH) as determined by SOM during the ERCP. Subjects that do not have PSH (pancreatic manometry normal) will receive either sham or biliary sphincterotomy. Subjects with PSH (pancreatic manometry abnormal) will receive either sham, biliary sphincterotomy or dual sphincterotomy. Details of the randomization scheme are in the Statistical Analysis Plan (SAP).

17.2.2 Descriptive Statistics

Univariate descriptive statistics and frequency distributions will be calculated, as appropriate, for all variables for each time point of measurement. Association between the outcome variables (primary and secondary) and the baseline values (at Month 0) for demographic, clinical, and laboratory parameters will be evaluated. These analyses will identify potential confounding variables to be used as covariates in subsequent analyses.

17.2.3 Missing Data

Under the intent-to-treat principle (ITT) principle, all subjects who are randomized are included in the analysis. Therefore, missing data, especially in the outcome measures, can be problematic. Although every attempt will be made to prevent incomplete data, a certain amount of missing data is inevitable due to losses to follow up or withdrawn consents. A thorough analysis of variables, reasons and patterns of missing data will be conducted. If a subject drops out of the study, the reason for drop out will be recorded and every effort to collect the remaining follow up data will be made. For the primary outcome, if both 9 and 12 month RAPID are missing or if only the 12-month RAPID is missing, then the subject is considered a treatment failure (even if Month 9 is Grade 1). However if the 9-month RAPID score is missing, but the 12-month and the 6-month RAPID scores are available, the 6-month result will be carried forward to the 9-month mark. If data on the re-intervention status (Yes/No) is missing then a subject will be considered a failure with respect to the primary outcome.

17.3 Statistical Analyses

As the primary analysis, all efficacy outcome measures will be analyzed under the intent-to-treat principle (ITT). The ITT sample will include all subjects who are randomized regardless of whether the subject actually receives the study intervention to which they were assigned (sphincterotomy or sham). Sensitivity analyses will be conducted by repeating the proposed analyses using the per protocol population which is defined as all randomized subjects who receive the study intervention to which they were assigned and who complete the 12 months of follow up to observe the characteristics of only true study completers. If

differences are present between this analysis and the primary ITT analysis, the characteristics of the two analysis populations will be examined to aid in explaining any discrepancies.

17.3.1 Interim Analysis

One interim analysis using the alpha spending function method (Lan & DeMets, 1987) with O'Brien and Fleming (OBF) type stopping guidelines (O'Brien & Fleming, 1979) and the stochastic curtailment method (Lan and Simon, 1982) will be used for the assessment of efficacy and futility, respectively, after approximately the first 71 consecutively randomized subjects complete the primary outcome assessment of success or failure (maximum of 12 months follow up). The interval may be more frequent if requested by DSMB. The trial may be stopped for overwhelming efficacy of one treatment group over the other at the interim analysis if the test statistic crosses the OBF boundary. We chose the OBF boundary because it is most frequently used to monitor clinical trials and is more conservative than the alternative Pocock boundary for both rejection and acceptance of the null hypothesis (Piantidosi, 1997). In addition, the alpha spending function method gives the flexibility of changing the intervals of monitoring while still preserving the overall Type I error rate (Lan & Demets, 1987). The stopping boundaries for overwhelming efficacy (illustrated below) were calculated using EAST® 5 software (Cytel Corporation). The SDMC will be responsible for conducting these analyses and compiling the reports for the DSMB.

Analysis	Approximate Sample Size	Minimum Test Statistic (Z value) to reject H_o	Boundary Crossing Probabilities Under H1
1	71	3.731	0.074
2 (Final)	214	1.961	0.916

The study may also be stopped for futility if, given the data up to the point of interim analysis, the probability of detecting a 30% benefit for the sphincterotomy group overall is < 20%. A conditional power less than 20% indicates that if we were to conduct a single (final) analysis of the data there is less than a 20% chance of detecting statistical significance. Since many factors need to be taken into consideration before stopping a study, the above are guidelines that will be followed; however, safety and study progress also will be taken into consideration by the Executive Committee and the DSMB in the decision to stop the study for either efficacy or futility.

17.3.2 Final Analysis

17.3.2.1 Primary Outcome

The primary statistical analysis will develop a logistic regression model with treatment group as the factor of interest and clinical center and SOM (normal/abnormal) as covariates. A chi-square test will be performed to compare the treatment group proportions using a two-tailed significance level of 0.05. The intent-to-treat principle will be used for the primary analysis and is defined as all persons randomized to one of the two interventions. Further details are located in the EPISOD Statistical Analysis Plan of the MoP.

Several procedures have been incorporated into the study design (i.e., procedure manual, re-intervention guidelines, blinding) to reduce center effects; however, these effects cannot be ignored for this trial. The distribution of center demographics will be examined. Means, standard deviations, proportions and 95% confidence intervals will be presented. Center and center*treatment interaction terms will be included in the primary analysis as well as all relevant analysis models with 'center' treated as a fixed effect. Center will be represented by 5 dummy variables and will always be included in the model. The interaction term will be omitted from the model if it is not statistically significant ($p > 0.15$).

17.3.2.2 Secondary Outcomes

This study is designed to test the primary hypothesis. However, it also offers the opportunity to conduct analyses to evaluate the diagnostic use of SOM, the pattern of episodic pain events in this sample as well as the association between these pain episodes and depression/anxiety.

17.3.2.2.1 Secondary Aim 1: In addition to testing the primary hypothesis, it is of clinical importance to evaluate the association between SOM results and the treatment outcome (Secondary Aim 1). The relationship between the initial SOM results (normal/abnormal) and the study outcome (success/failure) will be evaluated using a chi-square test with one degree of freedom. All subjects randomized to sphincterotomy will be included in this analysis. Studies in SOD II patients (Toouli et al, 2000; Geenen et al, 1989) showed > 85% of the patients with elevated sphincter pressures on manometry had a successful sphincterotomy and less than 62% with a normal sphincter pressure had a successful sphincterotomy. Using these results, it is hypothesized that knowing the result of SOM alters the probability that an SOD III patient will have a successful (or unsuccessful) response to

sphincterotomy. Thus roughly 128 subjects (accounting for drop out) will provide at least 90% power to test the null hypothesis of independence.

17.3.2.2.2 Secondary Aim 2: Also of clinical importance is to evaluate and compare the success rates of biliary and dual sphincterotomies (Secondary Aim 2). The subgroup (n~64) of subjects that has elevated sphincter pressures (PSH) and is randomized to either biliary or dual sphincterotomy will be evaluated. The success rates (as defined by the primary outcome) for each subgroup will be estimated using a 2-sided 95% binomial confidence interval and will be compared using a chi-square test for the comparison of two independent proportions. In addition, a logistic regression model adjusting for center effects and important prognostic variables identified during preliminary analyses (see below, Other Statistical Considerations) will be developed. Assuming 50% (n=96) of the randomized population has pancreatic sphincter hypertension (PSH) and based on the above percentage (10%) of drop-outs, it is anticipated that 64 PSH subjects will undergo either a dual (pancreatic and biliary) sphincterotomy or biliary sphincterotomy alone (assuming a 1:1 randomization). Based on clinical experience, roughly 40% of the subjects randomized to biliary sphincterotomy alone are expected to have a successful procedure (success defined as the primary outcome). If 32 subjects in each subgroup undergo the assigned procedure and follow up period, we will have 80% power to detect an absolute difference of 35% ($Sphinc_{bil}$=.40; $Sphinc_{dual}$=.75).

17.3.2.2.3 Secondary Aim 3: To address Secondary Aim 3, evaluating the effects of pre-specified prognostic factors on the primary outcome, a logistic regression model similar to the primary model will be developed using the dichotomous primary outcome, treatment success/failure. Treatment, center and PSH status will be main effects in the model. The following covariates will be examined: baseline anxiety and depression levels (HADS/BDI), baseline psychiatric diagnosis (MINI), age, gender, BMI, and presence/absence of functional digestive disorders. Each covariate will be assessed individually first with a model that includes interaction effect with the treatment. If a significant interaction is observed ($p < 0.15$), then subgroup analyses will be considered. All randomized subjects (n~214) will be included in this analysis. Parameter estimates will be evaluated at a two-sided type I error rate of 0.05. Odds ratios and two-sided 95% confidence intervals will be generated.

17.3.2.2.4 Secondary Aim 4: Since both SOD III and anxiety/depressive symptoms may be influenced by common neurochemical mediators, the change over time in depression and anxiety levels will be modeled using the follow up HADS scores. Repeated measures on the HADS will be examined to compare average scores across treatment groups over time while adjusting for baseline covariates identified in the preliminary analyses, including stratification variables. Change over time in severity and frequency of pain episodes (RAPID questions 6 and 7) as well as QOL (SF-36) also will be modeled. The Proc Mixed procedure in SAS V9 (SAS Institute, Cary, NC) will be used to model the covariance structure and to analyze time trends for treatments. Covariates included in the model will be treatment group, center, and time. Other covariates will be considered based on the results from the preliminary analyses. Linearity will be assessed and if necessary non-linear mixed models will be applied. Baseline values (Month 0) for these outcomes will be incorporated into each model to aid in explaining differences between the two treatment groups. Differences between intervention groups in terms of response over time will be assessed by evaluating the statistical significance of group-by-time interactions. All randomized subjects (n=214) will be included in this analysis.

17.3.2.2.5 Secondary Aim 5: The aim of the EPISOD Economic Study is to compare differences in medical resource use, cost effectiveness, and overall cost for the treatment approaches. The treatment groups will be compared on several economic measures.

18.0 ADVERSE EVENTS

18.1 DEFINITIONS OF ADVERSE EVENT AND SERIOUS ADVERSE EVENT

18.1.1 Adverse Event

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Each AE is a unique representation of a specific event used for medical documentation and scientific analysis.

18.1.2 Serious Adverse Event

An SAE is any AE that results in any of the following outcomes:

- Death,
- Life-threatening adverse experience,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that **may require medical or surgical intervention** to prevent one of the outcomes listed above,
- Event occurring in a gene therapy study,
- Event that changes the risk/benefit ratio of the study.

18.1.3 Life-Threatening Adverse Event

Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

18.2 SEVERITY OF AN ADVERSE EVENT

'Severity' is not the same as 'serious.' Serious is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. The term 'severe' is often used to describe the intensity (severity) of a specific event (as in mild, moderate, severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. Most AEs include clinical criteria that describe patient/event outcomes or indicated interventions to more clearly substantiate seriousness.

18.3 RELATIONSHIP TO STUDY TREATMENT

One of the most important components of AE reporting is determining the cause of the AE. It is imperative that the investigator assess AE causality in terms of overall study participation and make an independent **determination as to whether the AE was thought to be <u>related</u> to any study-related activity** (i.e., study intervention, test article administration, study-related tests or procedures). For each adverse event, the relationship to the study treatment must be recorded as one of the choices on the following scale:

Definitely Causal relationship is certain (i.e., the temporal relationship between treatment exposure and the adverse event onset/course is reasonable; there is a clinically compatible response to decaling; other causes have been eliminated; and the event must be definitive pharmacologically or phenomenological, using a satisfactory rechallenge procedure if necessary).

Probably High degree of certainty for causal relationship (i.e., the temporal relationship between treatment exposure and the adverse event onset/course is reasonable; there is a clinically compatible response to dechallenge [rechallenge is not required]; and other causes have been eliminated or are unlikely).

Possibly Causal relationship is uncertain (i.e., the temporal relationship between treatment exposure and the adverse event onset/course is reasonable or unknown; dechallenge/rechallenge information is either unknown or equivocal; and while other potential causes may or may not exist, a causal relationship to the study treatment does not appear probable).

Unlikely Not reasonably related, although a causal relationship cannot be ruled out (i.e., while the temporal relationship between treatment exposure and the adverse event onset/course does not preclude causality, there is a clear alternate cause that is more likely to have caused the adverse event than the study treatment).

Not related No possible relationship (i.e., the temporal relationship between treatment exposure and the adverse event onset/course is unreasonable or incompatible; or a causal relationship to study treatment is implausible).

Site investigators are responsible for documenting and maintaining documents regarding AEs that are determined to be unrelated to research participation in the research record for future follow-up, documentation and reference.

18.4 CLASSIFICATION OF ADVERSE EVENTS

For the purposes of this study, all complications will be referred to as Adverse Events (AEs).
There are 2 categories of possible adverse events in this study (defined in section 18.4.1 and 18.4.2):

These adverse events (defined in detail below) will be documented using 2 well-accepted lexicons which are described in detail in the following sections:

(1) ERCP Adverse Events Table for events definitely or probably related to ERCP
(2) NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used for events possibly, unlikely, and not related to ERCP.

18.4.1 ADVERSE EVENTS DIRECTLY RELATED TO ERCP

Adverse events directly related to ERCP include:

- Events that are common to all ERCP procedures; and,
- Events that are related to ERCP treatments.

ERCP Adverse Event Table: Any adverse event probably or definitely related to ERCP will be reviewed and assessed using the ERCP Adverse Events Table which describes and grades events based on a widely accepted clinical lexicon. A current version of the ERCP Adverse Events Table will be located in the Manual of Procedures on WebDCU™.

18.4.1.1 *Adverse Events Common to <u>All</u> ERCP Procedures*

- **<u>Pancreatitis</u>:** Pancreatitis is the most common side effect of an ERCP (5-10% of ERCPs). It occurs within 24 hours after the ERCP procedure and requires hospital admission. Symptoms of pancreatitis include pain, a swollen and tender abdomen, nausea, vomiting, fever and rapid pulse (heart rate). The treatment for mild pancreatitis consists of restriction of oral intake to ice chips, intravenous fluids, and analgesics. It usually settles in 1-3 days. However, very rare severe cases may result in formation of a pancreatic pseudocyst or abscess. The heart, lungs, or kidneys may fail.

- **<u>Cardio-pulmonary</u>:** The effects of sedation/anesthesia and the stresses of the ERCP procedure may result (during procedures or in the early recovery period) in pulmonary dysfunction (eg hypoxia, pneumonia), or cardiac compromise (eg dysrythmia, myocardial ischemia, infarction). Most of these events can be managed by standard conservative means, but some may result in the procedure being aborted, and/or the need for subsequent hospitalization

- **<u>Infection</u>:** Infection can occur in the bile ducts or pancreas after ERCP. This usually happens when there is obstruction to the bile or pancreatic ducts that cannot be treated by the ERCP procedure. This does not apply to these subjects with SOD, since obstruction has been excluded by prior imaging. When infection occurs, antibiotics will be required, and possibly another type of drainage procedure such as surgery.

- **<u>Reactions to Contrast Dye</u>**: The risk of an allergic reaction to the contrast dye is very small (<1:1000 cases), and can be minimized by pre-treating with steroids those subjects known to have iodine allergy. Reactions are usually mild (such as hives), but, very rarely, anaphylactic reactions can compromise breathing.

- **Other definitely or probably ERCP related events not listed above**

18.4.1.2 *Adverse Events Related to ERCP Treatments*

Specific therapeutic maneuvers performed at the time of ERCP carry certain risks in addition to the above adverse events common to all ERCP procedures.

- **Bleeding:** Biliary and pancreatic sphincterotomy can cause bleeding, which can usually be controlled during the ERCP. Blood transfusion may be needed after about 1% of sphincterotomies. Very rarely, another procedure (repeat ERCP, interventional radiology or surgery) may be required. Occasionally bleeding is delayed for up to 2 weeks after the procedure.

- **Perforation:** Sphincterotomy can result in a perforation when the cut extends into the tissues behind the duodenum and pancreas. The incidence is about 1%. Most perforations can be treated medically (with IV fluids, antibiotics, and nasogastric tube), but severe cases may require surgery. On very rare occasions, the endoscope itself can cause a perforation in the wall of the esophagus, stomach or intestine. This type of perforation usually requires surgical treatment.

- **Pancreatic Stent Problems.** Placement of a small pancreatic stent is very safe, but adverse events have occurred. There is a chance of <1:1000 that the stent could be placed within or migrate into the duct, and cause pancreatitis or infection. Migrated stents can be difficult to retrieve and even require surgery.

- **Risks for EGD**: When an EGD is performed to retrieve a pancreatic stent, t**here is a very small risk of pancreatitis and of adverse events due to sedation/anesthesia.**

- **Other definitely or probably ERCP related events not listed above**

18.4.2 ADVERSE EVENTS NOT related to ERCP

These include all events after ERCP which are classified (as in 18.3) as not related, or unlikely/possibly related. They will be reviewed, assessed and graded using the ***NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE):***
Details of CTCAE are given in the Manual of Procedures on WebDCU™.

The CTCAE provides a grading (severity*) scale for each AE term and AEs are listed alphabetically within categories based on anatomy or pathophysiology. The CTCAE (v 3.0) also displays Grades 1-5 with unique clinical descriptions of severity for each AE based on this general guidance:

Grade 1: Mild AE
Grade 2: Moderate AE

Grade 3: Severe AE
Grade 4: Life-Threatening or Disabling AE
Grade 5: Death related to AE

Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade Selection. Grade 5: Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

18.4.3 ALTERNATIVE GRADING SCALE

If for some reason an adverse event is not listed in either the ERCP or CTCAE table, the following system should be used to classify the event:

1 = Mild adverse event; did not require treatment
2 = Moderate adverse event, did not require treatment
3 = Severe adverse event; inability to carry on normal activities; required professional medical attention
4 = Life-threatening or permanently disabling adverse event
5 = Fatal adverse event

***Note:** **Severity** is not equivalent to **seriousness.** A **serious adverse event (SAE)** would be any event in category 4 or 5, and any event in category 3 that required or prolonged hospitalization.

18.5 ADVERSE EVENTS & SERIOUS ADVERSE EVENTS REPORTING PROCEDURES

18.5.1 Adverse Events Recording into the Study Database

All AEs and SAEs will be recorded on the online AE CRF through the WebDCU™. The PI or the Study Coordinator at each Clinical Site is responsible for entering any and all AEs and SAEs into the database as soon as he/she becomes aware of the event and updating the information (e.g., date of resolution, action taken) in a timely manner. In the least, all non-serious AEs that have occurred during the study period must be recorded on the electronic AE CRF within 5 days from the time it was discovered by the site study personnel. (All non-serious AEs during hospitalization must be entered within 5 days of discharge.) For SAEs, the data entry must take place within 24 hours of discovery of the event. Principal Investigators must review the SAE within 72 hours of notification of the event.

Upon completion of the study protocol by the subject, premature withdrawal from the study by the subject, or subject's death, all information regarding each AE must be completed, if not done so earlier.

18.5.2 Procedure for Reporting of Serious Adverse Events

The PI at each site is responsible for comprehensive oversight of subject safety through monitoring that includes careful assessment and classification of Adverse Events (AEs). Once classified as a serious adverse event (SAE), the reporting procedures described below will be followed.

18.5.3 Medical Safety Monitor

The site PI is responsible for beginning the reporting process of all SAEs within 24 HOURS of awareness of an SAE. All SAEs should be data entered into ***WebDCU™ within 24 hours of notification of the event. The PI must confirm knowledge of the SAE within 72 hours of notification of the event.*** Once this information is submitted to WebDCU™, the Medical Safety Monitor and the "Back-Up" Medical Safety Monitor (in case the primary Medical Safety Monitor is unreachable) will be notified. Details of the reporting requirements are outlined in the Safety Monitoring Plan housed in the MoP.

If a previous SAE not initially deemed reportable is later found to fit the criteria for reporting, the site must enter the information into WebDCU™ no later than 24 hours from the time the determination is made.

18.5.4 Investigator Responsibilities

Each site PI is responsible for reporting adverse events (including follow-up information) to the IRB in accordance with local IRB and institutional requirements. In addition, copies of all SAE reports and documentation regarding IRB notification must be kept in the Investigator's research record and must be accessible for review during site monitoring visits. For studies that have a DSMB, the investigator is required to forward summary reports to the IRB as soon as they are received.

18.5.5 Follow-up Reporting

Site study clinicians are responsible for monitoring and follow-up of all AEs until resolution and appropriate documentation in the subject research record is completed. In addition to performing protocol-specified follow-up, site clinicians must review all previously reported ongoing AEs to evaluate the current status. **This applies to all events regardless of seriousness**.

If an AE previously reported on an Adverse Event CRF increases in severity or the frequency worsens, it must be reported as a NEW AE by submitting a NEW ADVERSE EVENT CRF through WebDCU™.

All unresolved AEs must be documented/reported as follows:

- **Outcome:** Outcome must be documented/reported for the 1st AE to reflect increases in severity and/or worsening of frequency.

- **Outcome/Onset Date**: The OUTCOME of the first AE will also be the ONSET DATE of the new AE (date severity increased or frequency worsened).

18.5.6 Reporting Recurrent Adverse Events

If an AE that was previously reported on the Adverse Event CRF fully resolves and then recurs at a later date, the second occurrence is considered a new AE and a new Adverse Event CRF must be completed.

Likewise, if an SAE that was previously reported and subsequently fully resolved later recurs at a level requiring expedited reporting, the SAE must be reported as a new SAE on the Adverse Event CRF.

Resolution is the normalization or return to baseline of laboratory values, clinical signs or symptoms related to the event.

18.5.7 Site IRB Responsibilities

The IRB has the authority to suspend or terminate approval of research at its site that has been associated with unexpected serious harm to participants. When an IRB takes such action, it is required to provide a statement of reasons for the action and to promptly report this action to the investigator, appropriate institutional officials, the Department or Agency head, and Office for Protection from Research Risks (OPRR). An IRB should communicate concerns to the DSMB and/or the Institute sponsoring the study if it believes that the safety of study participants is in jeopardy.

18.5.8 Site Monitoring & SAE Reporting

During a monitoring visit, the Clinical Research Associate (CRA) for EPISOD will verify appropriate documentation and reporting of SAEs at each site. In addition, if the CRA identifies an unreported SAE appropriate documentation and reporting will be initiated as guided by the CRA.

19.0 REGULATORY AND ETHICAL OBLIGATIONS

19.1 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 or participant's legally

authorized representative 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 done 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 responsible for the conduct of the institution. All elements listed in the ICH Good Clinical Practice guidelines must be included in the informed consent.

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.

19.2 INSTITUTIONAL REVIEW BOARD (IRB)

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

19.2.1 Initial Review and Approval

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

19.2.2 Amendments

Protocol amendments may only be made with the prior approval of the Executive Committee. The Principal Investigator must agree to, and obtain approval from the IRB for, all protocol amendments and revisions to the informed consent document as dictated by Executive Committee. The Principal Investigator at each Clinical Center must obtain approval from the IRB for all revisions to the informed consent document, whether

initiated by the investigator or Executive Committee. The Principal Investigator should notify the IRB of serious adverse events occurring at the Clinical Center and other adverse event reports received from the Coordinating Center, in accordance with local procedures and Section 18.0 of this protocol.

19.2.3 Annual

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

19.3 PRE-STUDY DOCUMENTATION REQUIREMENTS

The Principal Investigator at each Clinical Center is responsible for forwarding all required regulatory documents to the EPISOD Coordinating Center for review PRIOR to recruitment (located in the current version of the Manual of Procedures on WebDCU™).

19.4 SUBJECT CONFIDENTIALITY

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

20.0 ADMINISTRATIVE AND LEGAL OBLIGATIONS

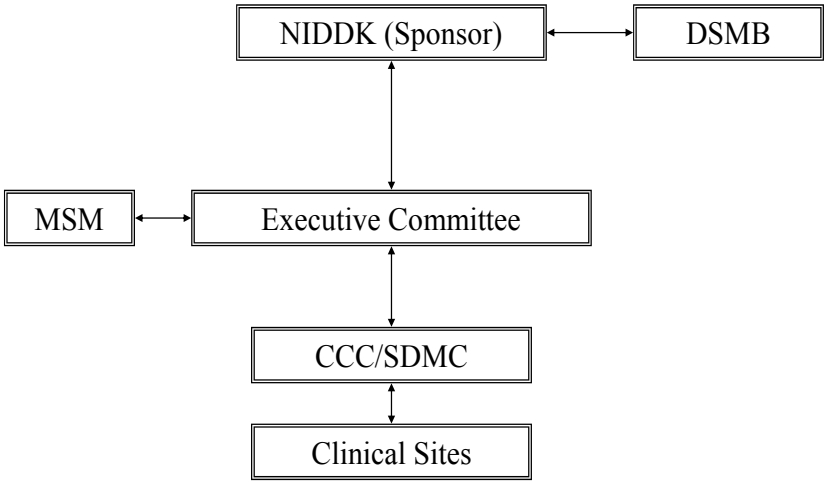
20.1 Study Termination

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 in writing of the trial's completion or early termination.

21.0 STUDY ORGANIZATION



* SDMC=Data Coordination Unit (DCU); CCC=Clinical Coordinating Center; MSM=Medical Safety Monitor

21.1 Executive Committee

The Executive Committee will prepare the final protocol and provide long-term scientific direction for the study at the operational level. The Executive Committee will advise and assist the CCC on operational matters, monitor the performance of the clinical centers and receive requests for any proposed ancillary changes in the protocol to the Project Scientist and the Data and Safety Monitoring Board (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., CCC, SDMC, clinical centers, Steering Committee, DSMB).

Throughout the study, the Executive Committee will meet every other week 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 EPISOD Manual of Procedures located on WebDCU™.

21.2 Steering Committee

The Steering Committee (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 once annually and in between as circumstances indicate. This committee's membership and list of duties/responsibilities is detailed in the current version of the EPISOD Manual of Procedures located on WebDCU™.

21.3 Coordinator Committee

The voting members of this group are the Coordinators from each Clinical Site; the nonvoting members are the SDMC staff and additional study coordinators who attend the meeting. The Coordinator Committee is responsible for providing information to the EPISOD trial PI regarding logistical aspects of the study protocol and procedures as they relate to each Clinical Site.

The Chairperson of the Coordinators' Group is responsible for preparing the agendas for meetings, based on comments and suggestions solicited from the group. The Chairperson is also a voting member of the EPISOD Executive Committee. Further details on this committee can be found in the current version of the EPISOD Manual of Procedures located on WebDCU™.

21.4 Exemption Committee: The Exemption Committee, a subcommittee of the Steering Committee, will adjudicate eligibility criteria that are brought to question by a participating clinical center. Meetings will convene on an as needed basis. Membership information is detailed in the current version of the current version of the EPISOD Manual of Procedures located on WebDCU™.

21.5 Publications Committee: The Publications Committee will develop, oversee and enforce Publication and Presentation policies and procedures. Membership information is detailed in the current version of the current version of the EPISOD Manual of Procedures located on WebDCU™.

21.6 Statistical and Data Management Center

The Statistical and Data Management Center (SDMC) is housed in the Department of Biostatistics, Bioinformatics and Epidemiology 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. The group has worked closely with Dr. Cotton on previous multicenter studies and continues this collaborative effort through this proposal.

21.7 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 EPISOD 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; on-going reviews of relevant SAE and DSMB reports, deviations, and all clinical data; and on-going support for study PIs and site staff for protocol-specific clarification and other feedback regarding safety throughout the EPISOD study.

21.8 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 NIDKK will appoint the DSMB members. 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 and Steering 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.

22.0 REFERENCES

1. Arguedas MR, Linder JD, and CM Wilcox. Suspected sphincter of Oddi dysfunction type II: Empirical biliary sphincterotomy or manometry-guided therapy? Endoscopy, 2004; 36(2): 179-82.
2. Ashby, J., The accuracy of cost measure derived from Medicare cost report data. Hospital Cost Management and Accounting, 1992. 3: p. 1-8.
3. Aymerich RR, Prakash C, Aliperti G. Sphincter of Oddi manometry: is it necessary to measure both biliary and pancreatic sphincter pressure? Gastrointest Endosc 2000; 52:183-6.
4. Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory-II. 1996. San Antonio, TX: Psychological Corporation.
5. Bennett EJ, Piesse C, Palmer K, Badcock CA, Tennant CC, Kellow JE.Functional gastrointestinal disorders: psychological, social, and somatic features. Gut. 1998;42(3):414-20.
6. Behar J, Corazziari E, Guelrud M, Hogan W, Sherman S, Toouli J. Functional Gallbladder and Sphincter of Oddi Disorders. Gastroenterology 2006; 130:1498-1509.
7. Beurskens AJ, de Vet HC, Koke AJ. Responsiveness of functional status in low back pain: a comparison of different instruments. Pain. 1996; 65: 71-76.
8. Blaut U, Sherman S, Fogel E, Lehman GA. Influence of cholangiography on biliary sphincter of Oddi manometric parameters. Gastrointest Endosc 2000; 52(5):129-40.
9. Blier P, Gobbi G, Haddjeri N, Santarelli L, Mathew G, Hen R. Impact of substance P receptor antagonism on the serotonin and norepinephrine systems: relevance to the antidepressant/anxiolytic response. J Psychiatry Neurosci. 2004;29(3):208-18.
10. Botoman VA, Kozarek RA, Novell LA, Patterson DJ, Ball TJ, Wechter DG, Neal LA. Long term outcome after endoscopic sphincterotomy in patients with biliary colic and suspected sphincter of Oddi dysfunction. Gastrointest Endosc 1994; 40:165-70.
11. Campo JV, Bridge J, Ehmann M, Altman S, Lucas A, Birmaher B, Di Lorenzo C, Iyengar S, Brent DA. Recurrent abdominal pain, anxiety, and depression in primary care. Pediatrics. 2004 A;113(4):817-24
12. Campo JV, Dahl RE, Williamson DE, Birmaher B, Perel JM, Ryan ND. Gastrointestinal distress to serotonergic challenge: a risk marker for emotional disorder?J Am Acad Child Adolesc Psychiatry. 2003;42(10):1221-6.
13. Campo JV, Perel J, Lucas A, Bridge J, Ehmann M, Kalas C, Monk K, Axelson D, Birmaher B, Ryan N, Di Lorenzo C, Brent DA. Citalopram treatment of pediatric recurrent abdominal pain and comorbid internalizing disorders: an exploratory study. J Am Acad Child Adolesc Psychiatry. 2004;43(10):1234-42.
14. Carlsson AM, Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analog scale. Pain 1983; 16: 87.
15. Chan YK, Evans PR, Dowsett JF, Kellow JE, Badcock CA. Discordance of pressure recordings from biliary and pancreatic duct segments in patients with suspected sphincter of Oddi dysfunction. Dig Dis Sci 1997; 42:1501-6.
16. Chaudhary, M.A. and Stearns, S.C., Estimating confidence intervals for cost-effectiveness ratios: an example from a randomized trial. Stat Med, 1996. 15(13): p. 1447-58.

17. Chen YK, Evans PR, Dowsett JF, Kellow JE, Badcock CA. Discordance of pressure recordings from biliary and pancreatic duct segments in patients with suspected sphincter of Oddi dysfunction. Dig Dis Sci 1997; 42:1501-6.
18. Cicala M, Habib FI, Vavassori P, Pallotta N, Schillaci O, Costamagna G, et al. Outcome of endoscopic sphincterotomy in post cholecystectomy patients with sphincter of Oddi dysfunction as predicted by manometry and quantitative choledochoscintigraphy. Gut 2002; 50:665-68.
19. Cohen S, Bacon BR, Berlin JA, Fleischer D, Hecht GA, Loehrer PJ, McNair AE, Mulholland M, et al. National Institutes of Health State-of-the-Science Conference Statement: ERCP for diagnosis and therapy, January 14-16, 2002. Gastrointest Endosc 2002; 56(6):803-9.
20. Corazziari E, Shaffer EA, Hogan W, Sherman S, Toouli J. Functional disorders of the biliary tract and pancreas. Gut 1999; 45:48-54.
21. Cotton PB, Lehman G, Vennes J et al. Endoscopic sphincterotomy, complications and their management. An attempt at consensus. Gastrointestinal Endoscopy. 37(3):383-93, 1991.
22. Cotton PB. Is your sphincterotomy really safe—and necessary? Gastrointest Endosc 1996; 44(6):752-5.
23. Cotton PB. ERCP is most dangerous for people who need it least. Gastrointest Endosc 2001; 54(4):535-6.
24. Cotton, PB, Durkalski VL, Pineau BC, Palesch YY, Mauldin, PD, et al. "Virtual colonoscopy (CT colonography. A multicenter comparison with standard colonoscopy for detection of mass lesions." JAMA, 2004; 291(14): 1713-1719.
25. Cotton PB, Leung JWC. Advanced Digestive Endoscopy; ERCP. 2005 Blackwell publishing.
26. Coyle WJ, Pineau BC, Tarnasky PR, Knapple WL, Aabakken L, Hoffman BJ, Cunningham JT, Hawes RH, Cotton PB. Evaluation of unexplained acute and acute recurrent pancreatitis using endoscopic retrograde cholangiopancreatography, sphincter of Oddi manometry and endoscopic ultrasound. Endoscopy 2002; 34(8):617-23.
27. Craig AG, Peter D, Saccone GTP, Ziesing P, Wycherley A, Toouli J. Scintigraphy versus manometry in patients with suspected biliary sphincter of Oddi dysfunction. Gut 2003; 52:352-57.
28. Desautels SG, Slivka A, Hutson WR, Chun A, Mitrani C, DiLorenzo C, Wald A. Postcholecystectomy pain syndrome: pathophysiology of abdominal pain in sphincter of Oddi type III. Gastroenterology. 1999;116(4):900-5.
29. Deviere J et al., Nonresorbable copolymer implantation for gastroesophageal reflux disease: a randomized sham-controlled multicenter trial.. Gastroenterology. 2005 Mar;128(3):532-40.
30. Di Lorenzo C, Colletti RB, Lehmann HP, Boyle JT, Gerson WT, Hyams JS, Squires RH Jr, Walker LS, Kanda PT; AAP Subcommittee; NASPGHAN Committee on Chronic Abdominal Pain Chronic Abdominal Pain In Children: a Technical Report of the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2005;40(3):249-61.
31. Drossman DA, Li Z, Leserman J, Toomey TC, Hu YJ. Health status by gastrointestinal diagnosis and abuse history. Gastroenterology. 1996; 110:999-1007.

32. Drossman DA, Leserman L, Li Z, Keefe F, Hu YB, Toomey TC. Effects of Coping on Health Outcome Among Women With Gastrointestinal Disorders. Psychosomatic Medicine. 2000; 62:309-317.
33. Drossman DA, Toner BB, Whitehead WE, Diamant NE, Dalton CB, Duncan S, Emmott S, Proffitt V, Akman D, Frusciante K, Le T, Meyer K, Bradshaw B, Mikula K, Morris CB, Blackman CJ, Hu Y, Jia H, Li JZ, Koch GG, Bangdiwala SI.Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders. Gastroenterology. 2003;125(1):19-31.
34. Drossman DA, Whitehead WE, Toner BB, Diamant N, Hu YJ, Bangdiwala SI, Jia H. What determines severity among patients with painful functional bowel disorders?Am J Gastroenterol. 2000;95(4):974-80.
35. Drossman DA. The functional gastrointestinal disorders and the Rome II process. Gut 1999; 45(II):II1-5.
36. Drossman DA, Creed FH Olden KW, Svedlund J, Toner BB, Whitehead WE Pyschosocial aspects of the functional gastrointestinal disorders Gut 1999 45 (suppl) II25-II30
37. Dworkin RH, Turk DC, Farrar JT, Haythornwaite JA et al..Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005;113 (1-2):9-19.
38. Efron, B. and Tibshirani, R.J., An Introduction to Bootstrap. 1993, New York.: Chapman and Hall.
39. Epstein, A.M. and al., e., Costs of medical care and out-of-pocket expenditures for persons with AIDS in the Boston Health Study. Inquiry, 1995. 32: p. 211-221.
40. Evans PR, Dowsett JF, Bak YT, Chan YK, Kellow JE. Abnormal sphincter of Oddi response to cholecystokinin in postcholecystectomy syndrome patients with irritable bowel syndrome: the irritable sphincter. Dig Dis Sci 1995; 40:1149-56.
41. Eversman D, Fogel EL, Rusche M, Sherman S, Lehman GA. Frequency of abnormal pancreatic and biliary sphincter manometry compared with clinical suspicion of sphincter of Oddi dysfunction. Gastrointest Endosc 1999; 50:637-41.
42. Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole M. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001; 94:149-58.
43. Farrar JT. What is clinically meaningful: outcome measures in pain clinical trials. Clin J Pain 2000; 16:S106-12.
44. Fitzpatrick R, Ziebland S, Jenkinson C, Mowat A. A comparison of the sensitivity to change of several health status instruments in rheumatoid arthritis. J Rheum 1993; 20(3):429-36.
45. Fogel EL, Eversman D, Jamidar P, Sherman S, Lehman GA. Sphincter of Oddi dysfunction: pancreaticobiliary sphincterotomy with pancreatic stent placement has a lower rate of pancreatitis than biliary sphincterotomy alone. Endoscopy 2002; 34:280-5.
46. Fogel EL, Sherman S, Bucksot L, Shelly L, Lehman GA. Effects of droperidol on the pancreatic and biliary sphincters. Gastrointest Endosc 2003; 58(4):488-92.
47. Fogel EL, McHenry L, Sherman S, Watkins JL, Lehman GA. Therapeutic biliary endoscopy. Endoscopy 2005; 37(2):139-45.
48. Fogel EL, Eversman D, Jamidar P, Sherman S, Lehman GA. Sphincter of Oddi dysfunction: pancreaticobiliary sphincterotomy with pancreatic stent placement has a

lower rate of pancreatitis than biliary sphincterotomy alone. Endoscopy 2002; 34(4):280-5.
49. Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. Gastrointest Endosc 2004; 59(7):845-64.
50. Freeman ML, Nelson DB, Sherman S, et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med 1996; 335:909-18.
51. Freeman ML, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, et al. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. Gastrointest Endsoc 2001; 54:425-34.
52. Freeman ML. Understanding risk factors and avoiding complications with endoscopic retrograde cholangiopancreatography. Curr Gastroenterol Rep 2003; 5(2):145-53.
53. Freeman ML, Overby C, Dongfeng Q. Pancreatic stent insertion: consequences of failure and results of a modified technique to maximize success. Gastrointest Endosc 2004; 59:8-14.
54. Freeman ML, Guda NM. Endoscopic biliary and pancreatic sphincterotomy. Curr Treat Options Gastroenterol 2005; 8(2):127-34.
55. Geenen JE, Hogan WJ, Dodds WJ, et al. The efficacy of endoscopic sphincterotomy after cholecystectomy in patients with sphincter of Oddi dysfunction. N Engl J Med 1989; 320:82-7.
56. Gold, M.R., Siegel, J.E., Russell, L.B., and Weinstein, M.C., Cost-effectiveness in health and medicine. 1996, New York: Oxford University Press
57. Goldsmith CH, Boers M, Bombardier C, Tugwell P. Criteria for clinically important changes in outcomes: development, scoring and evaluation of rheumatoid arthritis patient and trial profiles. OMERACT Committee. J Rheumatol 1993; 20:561-65.
58. Gorelick A, Barnett J, Chey W, Anderson M, Elta G. Botulinum toxin injection after biliary sphincterotomy. Endoscopy. 2004 Feb;36(2):170-3.
59. Guda NM, Freeman ML. True Culprit or guilt by association? Is sphincter of Oddi manometry the cause of post-ERCP pancreatitis in patients with suspected sphincter of Oddi dysfunction, or is it the patients' susceptibility? Rev Gastroenterol Disord 2004; 4(4):211-13.
60. Guthrie E, Barlow J, Fernandes L, Ratcliffe J, Read N, Thompson Changes in tolerance to rectal distension correlate with changes in psychological state in patients with severe irritable bowel syndrome. Psychosom Med. 2004;66(4):578-82
61. Guy W. Clinical Global Impressions. New clinical drug evaluation unit (ECDEU) assessment manual for psychopharmacology. Washington, DC.1976; 218-222
62. Halder SL, McBeth J, Silman AJ, Thompson DG, Macfarlane GJ.Psychosocial risk factors for the onset of abdominal pain. Results from a large prospective population-based study. Int J Epidemiol. 2002;31(6):1219-25
63. Hebert R, Palesch Y, Aabakken L, Hennessey W, Mauldin PD, and PB Cotton. DDQ-15: a health-related quality of life instrument for patients with digestive disorders: self-administration by paper versus computer. Health Services and Outcomes Research Methodology, 2001; 2: 137-156.
64. Heymann-Monnikes I, Arnold R, Florin I, Herda C, Melfsen S, Monnikes H.The combination of medical treatment plus multicomponent behavioral therapy is superior to

medical treatment alone in the therapy of irritable bowel syndrome. Am J Gastroenterol. 2000;95(4):981-94.
65. Hillsley K, Mawe GM5-HT is present in nerves of guinea pig sphincter of Oddi and depolarizes sphincter of Oddi neurons. Am J Physiol. 1998;275(5 Pt 1):G1018-27.
66. Hogan WJ, Geenen JE. Biliary dyskinesia. Endoscopy. 20 Suppl 1:179-83, 1988
67. Hogan W, Sherman S, Pasricha P, Carr-Locke DL. Sphincter of Oddi manometry. Gastrointest Endosc 1997; 45:342-8.
68. Hogan WJ. Hepatobiliary scintigraphy as the diagnostic test for sphincter of Oddi dysfunction: pan the scan? Am J Gastroenterol 2002; 97(6):1288-91.
69. Holman H, Bloch DA, Lorig K, Laurent D. What is a 'clinically meaningful' reduction in pain? Pain 2001; 94:131-2.
70. Holmes A, Heilig M, Rupniak NM, Steckler T, Griebel G.Neuropeptide systems as novel therapeutic targets for depression and anxiety disorders. Trends Pharmacol Sci. 2003;24(11):580-8.
71. Howell S, Poulton R, Caspi A, Talley NJ.Relationship between abdominal pain subgroups in the community and psychiatric diagnosis and personality. A birth cohort study. J Psychosom Res. 2003;55(3):179-87
72. Jacob L, Geenen JE, Catalano MF, Geenen DJ. Prevention of pancreatitis in patients with idiopathic recurrent pancreatitis: a prospective nonblinded randomized study using endoscopic stents. Endoscopy 2001; 33:559-62.
73. Jagannath SB, Singh VK, Cruz-Correa M, Canto MI, Kalloo AN. A long-term cohort study of outcome after cholecystectomy for chronic acalculous cholecystitis. Am J Surg 2003; 185(2):91-5.
74. Jagannath S, Kalloo AN. Efficacy of biliary scintigraphy in suspected sphincter of Oddi dysfunction. Curr Gastroenterol Rep 2001; 3(2):160-5.
75. Jones MP, Maganti K. Symptoms, gastric function, and psychosocial factors in functional dyspepsia J Clin Gastroenterol. 2004;38(10):866-72
76. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. J Clin Epidemiol 1994; 47:81-7.
77. Kalloo AN, Tietjen TG, Pasricha PJ. Does intrabiliary pressure predict basal sphincter of Oddi pressure? A study in patients with and without gallbladders. Gastrointest Endosc 1996; 44(6):696-9.
78. Kalloo AN. Overview of differential diagnoses of abdominal pain. Gastrointest Endosc 2002; 56(6 Suppl):S255-7.
79. Kalloo AN, Pasricha PJ. Therapy of sphincter of Oddi dysfunction. Gastrointestinal Endoscopy Clinics of North America. 6(1):117-25, 1996
80. Kane RL, Bershadsky B, Lin W-C, Rockwood T, Wood K. Efforts to standardize the reporting of pain. J Clin Epidemiol 2002; 55:105-10.
81. Katz J, Melzack R. Measurement of pain. Surg Clin North Am 1999; 79(2):231-52.
82. Keefe FJ, Williams DA. A comparison of coping strategies in chronic pain patients in different age groups. J Gerontol 1990; 45:P 161–5
83. Kellow JE. Sphincter of Oddi dysfunction type III: another manifestation of visceral hyperalgesia? Gastroenterology 1999; 116(4):996-1000.
84. Khuroo MS, Zargar SA, Yattoo GN. Efficacy of nifedipine therapy in patients with sphincter of Oddi dysfunction: a prospective, double-blind, randomized, placebo-controlled, cross over trial. Br J Clin Pharmacol. 1992 May; 33(5):477-85

85. Killeen, T.K., Brady, K.T., Gold, P.B., Tyson, C., and Simpson, K.N., Comparison of self-report versus agency records of service utilization in a community sample of individuals with alcohol use disorders. Drug and Alcohol Dependence, 2004. 73: p. 141-147. participant and physician intervention preferences on randomized trials. JAMA 2005; 293(9):1089-99.
86. Koloski NA, Talley NJ, Boyce PMEpidemiology and health care seeking in the functional GI disorders: a population-based study. Am J Gastroenterol. 2002;97(9):2290-9
87. Lan, K.K.G. and DeMets, D.I., Design and analysis of group sequential tests based on type-I error spending rate function. Biometrika, 1987. 74: p.149-54.
88. Lan, K.K.G., Simon, R., and Halperin, M., Stochastically curtailed tests in long-term clinical trials. Communications Stat-Sequential Analysis, 1982. 1: p. 207-19.
89. Landrum K, Welch L. TIME: Toolkit of instruments to measure endo-of-life care. Pain and physical symptoms. www.chcr.brown.edu/pcoc/Physical.htm.
90. Larson TR, Blute ML, Bruskewitz RC, Mayer RD, Ugarte RR, Utz WJ. A high-efficiency microwave thermoablation system for the treatment of benign prostates hyperplasia: results of a randomized, sham-controlled, prospective, double-blind, multicenter clinical trial. Urology 1998; 51:731-42.
91. Lee JS, Bailey MJ, Jeong J, Mauldin PD, Weintraub WS. A study on the cost-effectiveness of coronary revascularization mimic health status model. Health Economics 1997; 6:613-623.
92. Leserman J, Li Z, Drossman DA, Toomey TC, Nachman G, Glogau L. Impact of Sexual and Physical Abuse Dimensions on Health Status: Development of an Abuse Severity Measure. Psychosomatic Medicine, 1997; 59:152-160.
93. Leserman J, Li Z, Drossman DA, Toomey TC, Nachman G, Glogau L. Sexual and physical abuse history in gastroenterology practice: how types of abuse impact health status. Psychosom Med. 1996; 58: 4-15.
94. Linder JD, Geels W, Wilcox CM. Prevalence of sphincter of Oddi dysfunction: can results from specialized centers be generalized? Dig Dis Sci 2002; 47(11):2411-5.
95. Linder JD, Klapow JC, Linder SD, Wilcox CM. Incomplete response to endoscopic sphincterotomy in patients with sphincter of Oddi dysfunction: evidence for a chronic pain disorder. Am J Gastroenterol 2003; 98:1738-43.
96. Lipton RB, Stewart WF, Sawyer MB, Edmeads JG. Clinical Utility of an Instrument Assessing Migraine Disability: The Migraine Disability Assessment (MIDAS) Questionnaire. Headache 2001; 41: 854-861.
97. Lydiard RB, Greenwald S, Weissman MM, Johnson J, Drossman DA, Ballenger JC.Panic disorder and gastrointestinal symptoms: findings from the NIMH Epidemiologic Catchment Area project. Am J Psychiatry. 1994;151(1):64-70
98. Madura JA, Madura JA II, Sherman S, Lehman GA. Surgical sphincteroplasty in 446 patients. Arch Surg 2005; 140:504-512.
99. Maldonado ME, Brady PG, Mamel JJ, Robinson B. Incidence of pancreatitis in patients undergoing sphincter of Oddi manometry (SOM). Am J Gastroenterol 1999; 94:387-90.
100. Mauldin, P.D., Weintraub, W.S., and Becker, E.R., Predicting hospital costs for first-time coronary artery bypass grafting from pre-operative and post-operative variables. Am J Card, 1994. 74: p. 772-775.

101. Mauldin PD, Weintraub WS, Jeong J, and Becker ER. A Multiple Outcome Model to Assess Cost-Effectiveness: Results from the Emory Angioplasty versus Surgery Trial (EAST). Biometrical Journal 1999; 1: 3-23.
102. Mayer EA, Craske M, Naliboff BD. Depression, anxiety, and the gastrointestinal system. J Clin Psychiatry. 2001;62 Suppl 8:28-36;
103. McDowell I, Newell C. Pain Measurements. Chapter in: Measuring Health. A guide to rating scales and questionnaires. 2nd ed., New York, Oxford University Press, 1996
104. Menees S, Elta GH. Sphincter of Oddi dysfunction. Curr Treat Options Gastroenterol 2005; 8(2):109-15.
105. Mergener K, Kozarek RA. Therapeutic pancreatic endoscopy. Endoscopy 2005; 37(3):201-7.
106. Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody B, Kuykendall DH, Hollingsworth JC, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 2002; 347:81-88.
107. Mourits MP, van Kempen-Harteveld ML, Garcia MB, Koppeschaar HPF, Tick L, Terwee CB. Lancet 2000; 355:1505-9.
108. Neoptolemos JP, Bailey IS, Carr-Locke DL. Sphincter of Oddi dysfunction: results of treatment by endoscopic sphincterotomy. Br J Surg 1988; 75:454-59.
109. Niiyama H, Jagannath S, Kantsevoy S, Cruz-correa M, Magee C, Kalloo AN. Intrasphincteric nitric oxide reduces sphincter of Oddi motiligy in an endoscopic procine model. Dig Dis Sci 2003; 48(11):2187-90.
110. O'Brien, P.C. and Fleming, T.R., A multiple testing procedure for clinical trials. Biometrics, 1979. 35: p. 549-56.
111. Okolo P, Sherman S, Lehman GA, Lovett e. Psychometric profiles of patients with sphincter of Oddi dysfunction. Gastrointest Endosc. 1994; 40:P119.
112. Owen, J.E., Klapow, J.C., Hicken, B., and Tucker, D.C., Psychosocial interventions for cancer: review and analysis using a three-tiered outcomes model. Psychooncology, 2001. 10(3): p. 218-30
113. Park SH, Watkins JL, Fogel EL, Sherman S, Lazzell L, Bucksot L, Lehman GA. Long-term outcome of endoscopic dual pancreatobiliary sphincterotomy in patients with manometry-documented sphincter of Oddi dysfunction and normal pancreatogram. Gastrointest Endosc 2003; 57(4):483-91.
114. Pasricha PJ, Miskovsky EP, Kalloo AN. Intrasphincteric injection of botulinum toxin for suspected sphincter of Oddi dysfunction. Gut 1994; 35:1319-21.
115. Pasricha PJ. There is no role for ERCP in unexplained abdominal pain of pancreatico-biliary origin. Gastrointest Endosc 2002; 56(6) Supplement:S267-72.
116. Petersen BT. An evidence-based review of sphincter of Oddi dysfunction: part 1, presentations with "objective" biliary findings (types I and II). Gastrointest Endosc 2004; 59(4):525-34.
117. Petersen BT. Sphincter of Oddi dysfunction, part 2: evidence-based review of the presentations, with "objective" pancreatic findings (types I and II) and of presumptive type III. Gastrointest Endosc 2004; 59(6):670-87.
118. Piantidosi. Clinical Trials: A Methodologic Perspective. John Wiley& Sons, Inc., Chapter 10, 1997.

119. Piccinni G, Angrisano A, Testini M, Bonomo GM. Diagnosing and treating sphincter of Oddi dysfunction. A critical literature review and reevaluation. J Clin Gastroenterol 2004; 38(4):350-59.
120. Pineau BC, Knapple WL, Spicer KM, Gordon L, Wallace M, Hennesy WS, et al. Cholecystokinin-stimulated mebrofenin (^{99m}Tc-Choletec) hepatobiliary scintigraphy in asymptomatic postcholecystectomy individuals: assessment of specificity, interobserver reliability, and reproducibility. Am J Gastroenterol 2001; 96:3106-9.
121. Quallich LG, Stern MA, Rich M, Chey WD, Barnett JL, Elta GH. Bile duct crystals do not contribute to sphincter of Oddi dysfunction. Gastrointest Endosc 2002; 55:163-66.
122. Rashdan A, Fogel E, McHenry L Jr, Lehman G, Sherman S. Frequency of biliary crystals in patients with suspected sphincter of Oddi dysfunction. Gastrointest Endosc 2003; 58(6):875-8.
123. Rosenblatt ML, Catalano MF, Alcocer E, Geenen JE. Comparison of sphincter of Oddi manometry, fatty meal sonography, and hepatobiliary scintigraphy in the diagnosis of sphincter of Oddi dysfunction. Gastrointest Endosc 2001; 54(6):697-704.
124. Salem M, Rotevatn S, Stavnes S, Brekke M, Vollset SE, Nordrehaug JE. Usefulness and safety of percutaneous myocardial laser revascularization for refractory angina pectoris. Am J Cardiol 2004; 93:1086-91.
125. Sand J, Tainio H, Nordback I. Peptidergic innervation of human sphincter of Oddi. Dig Dis Sci. 1994;39(2):293-300.
126. Sand J, Nordback I, Koskinen M, Matikanainen M, Lindholm TS. Nifedipine for suspected Type II sphincter of Oddi dyskinesia. Am J Gastroenterol 1993; 38(4):530-35.
127. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC: The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22-33.
128. Sherman S, Gottlieb K, Uzer MF, Smith MT, Khusro QE, Earle DT, Brunelle RL, Hawes RH, Lehman GA. Effects of meperidine on the pancreatic and biliary sphincter. Gastrointest Endosc 1996; 44(3):239-42.
129. Sherman S, Ruffolo TA, Hawes RH, Lehman GA. Complications of endoscopic sphincterotomy: a prospective series with emphasis on the increased risk associated with sphincter of Oddi dysfunction and nondilated bile ducts. Gastroenterology 1991; 101:1068-75.
130. Sherman S, Lehman GA. Sphincter of Oddi dysfunction: diagnosis and treatment. J Pancreas 2001; 2(6):382-400.
131. Sherman S. What is the role of ERCP in the setting of abdominal pain of pancreatico-biliary origin (suspected sphincter of Oddi dysfunction)? Gastrointest Endosc 2002; 56 (6) Supplement:S258-266.
132. Sostre S, Kalloo AN, Spiegler EJ, Camargo EE, Wagner HN Jr. A noninvasive test of sphincter of Oddi dysfunction in postcholecystectomy patients: the scintigraphic score. J Nucl Med 1992; 33(6):1216-22.
133. Stewart WF, Lipton RB, Dowson AJ, Sawyer J.. Development and testing of the Migraine Disability Assessment (MIDA) questionnaire to assess headache related disability. Neurology 2001; 56(6): 20S – 28.

134. Talley SJ, Bytzer P, Hammer J, Young L, Jones M, Horowitz M.Psychological distress is linked to gastrointestinal symptoms in diabetes mellitus. Am J Gastroenterol. 2001;96(4):1033-8
135. Thune A, Scicchitano J, Roberts-Thomson I, Toouli J. Reproducibility of endoscopic sphincter of Oddi manometry. Dig Dis Sci 1991; 36(10):1401-5.
136. Toouli J, Roberts-Thomson IC, Kellow J, Dowsett J, Saccone GTP, Evans P, et al. Manometry based randomized trial of endoscopic sphincterotomy for sphincter of Oddi dysfunction. Gut 2000; 46:98-102.
137. Topazian M, Hong-Curtis J, Li J, Wells C. Predictors of outcome in post-cholecystectomy pain. Gastrointestinal Endoscopy 57(5): AB201, 2003.
138. Topazian M, Hong-Curtis J, Li J, Wells C. Improved predictors of outcome in postcholecystectomy pain. J Clin Gastroenterol 2004; 38(8):692-96.
139. Tourangeau, R. and Rasinski, K.A., Evaluation of Data Collection Frequency and the Use of a Summary in the National Medical Utilization and Expenditure Survey. Medical Care Utilization and Expenditure Survey, Series A. 1987, U.S. Government Printing Office: Washington, DC.
140. Varadarajulu S., and RH Hawes. Key issues in sphincter of Oddi dysfunction. Gastrointest Endoscopy Clin N Am. 13 : 671-694, 2003.
141. Varadarajulu S, Hawes RH, Cotton PB. Determination of sphincter of Oddi dysfunction in patients with prior normal manometry. Gastrointest Endosc 2003; 58(3):341-4.
142. Viceconte G, Micheletti A. Endoscopic manometry of sphincter of Oddi: its usefulness for the diagnosis and treatment of benign papillary stenosis. Scand J Gastroenterol 1995; 30:797-803.
143. Von Korff M, Ormal J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. Pain 1992; 50:133-49.
144. Walker EA, Roy-Byrne PP, Katon WJ, Li L, Amos D, Jiranek G. Psychiatric illness and irritable bowel syndrome: a comparison with inflammatory bowel disease. Am J Psychiatry. 1990;147(12):1656-61
145. Walker EA, Katon WJ, Jemelka RP, Roy-Bryne PP.Comorbidity of gastrointestinal complaints, depression, and anxiety in the Epidemiologic Catchment Area (ECA) Study.Am J Med. 1992;92(1A):26S-30S.
146. Ware JE. Standards for validating health measures: definition and content. J Chron Dis; 40:473-80, 1987.
147. Wehrmann T, Wiemer K, Lembeke B, et al. Do patients with sphincter of Oddi dysfunction benefit from endoscopic sphincterotomy? A five-year prospective trial. Eur J Gastroenterol Hepatol 1996; 8:251-6.
148. Wehrmann T, Seifert H, Seipp M, Lembcke B, Caspary WF. Endoscopic injection of botulinum toxin for biliary sphincter of Oddi dysfunction. Endoscopy. 30(8):702-7, 1998
149. Wilcox CM, Linder J. Prospective evaluation of droperidol on sphincter of Oddi motility. Gastrointest Endosc 2003; 58(4):483-7.
150. Wunderlich GR, Raymond R, DeSousa NJ, Nobrega JN, Vaccarino FJ.Decreased CCK(B) receptor binding in rat amygdala in animals demonstrating greater anxiety-like behavior. Psychopharmacology (Berl). 2002;164(2):193-9.

151. Zigmond AS, Snaith RP: The Hospital Anxiety and Depression Scale. Acta Psychiatrica Scandinavica. 1983; 67, 361-3700.