Evaluating **P**redictors & **I**nterventions in **S**phincter of **O**ddi **D**ysfunction:
EPISOD2
A Naturalistic Follow-Up Study

STUDY GROUP CHAIR
Peter B. Cotton, M.D.
Medical University of South Carolina

Supported by:

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Investigators' Agreement

I have read the attached clinical protocol titled " Evaluating Predictors & Interventions in Sphincter of Oddi Dysfunction: The EPISOD2 Trial, A Naturalistic Follow-Up Study " 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.

_____ _____

Signature of Principal Investigator Date

_____

Printed name of Principal Investigator

_____ _____

Signature of Co-Principal Investigator (When applicable) Date

_____

Printed name of Co-Principal Investigator (When applicable)

TABLE OF CONTENTS

1. SUMMARY

Protocol Title	Evaluating Predictors & Interventions in Sphincter of Oddi Dysfunction
Acronym	EPISOD2
Study Sites	Six to Ten clinical sites in US
Study Period	Planned enrollment period – 3 years; Planned duration of the study – 5 years
Study Population	SOD III Patients who MEET ELIGIBILITY REQUIREMENTS for the randomized EPISOD trial but decline participation.
Primary Study Objective	To conduct a careful follow-up study of standard of care treatment in a limited number of patients who decline randomization in the larger randomized EPISOD trial
Study Design	Open label cohort study
Sample Size	A maximum of 100 subjects with no site entering more than 5 consecutive subjects per year during the enrollment period (Years 1-3).
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 upper level of normal (ULN). ● Transaminase levels can be no more than 3 X upper limit of normal. 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 medication 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. 14. Declined participation in the EPISOD trial.

	15. 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 to severe depression defined by the 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;, d. e. Suicidal risk (equal to or greater than "low") using the MINI suicide section or a score of greater than 0 on question 9 of the BDI-II. 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	Standard of care ERCP with manometry and treatment by sphincterotomy, Botox injection or stenting.

The **E**valuating **P**redictors & **I**nterventions in **S**phincter of **O**ddi **D**ysfunction Naturalistic Follow-Up Trial (EPISOD2) is a prospective, observational study that will assess the value of standard of care ERCP as a treatment for adult subjects suffering from *episodes of abdominal* pain after cholecystectomy and categorized as Sphincter of Oddi dysfunction type III (SOD III).

Based on data from other endoscopic and surgical trials conducted with sham arms, in addition to correspondence with some of the authors (Salem et al., 2004; Mourits et al., 2000; Larson et al., 1998; Moseley et al., 2002; Deviere et al, 2005), it is anticipated that approximately 50% of *eligible* subjects will decline participation in the primary randomized

EPISOD trial. Patients who decline participation in EPISOD will receive standard current treatment, i.e., with sphincterotomy based on the results of SOM.

In an effort to provide structured outcome data on standard of care management for SOD III, and to assist in the interpretation of results for the randomized EPISOD trial, patients who decline participation in the randomized EPISOD trial will be invited to participate in a simple follow-up study (EPISOD2). Although EPISOD2 will use the same instruments as used in the larger, randomized EPISOD trial, instruments will be administered less frequently; i.e. baseline, and months 1, 6, 9 and 12.

A maximum of 100 subjects will be enrolled into EPISOD2, with no center entering more than 5 consecutive subjects per year during the enrollment period (Years 1-3). The rationale for restricting enrollment per center per year is to reduce potential temporal and selection bias. All subjects enrolled in EPISOD2 will receive standard of care treatment.

2. OBJECTIVES

To conduct a careful follow-up study of standard of care treatment in a limited number of patients who decline randomization in the larger randomized EPISOD trial. The data from EPISOD2 will be used to assist in the interpretation and assessment of generalizability of the primary aim and several secondary aims of the larger randomized EPISOD trial. Outcomes to be assessed include: (1) 12-month success rate (success defined as a Grade 1 on the Months 9 and 12 RAPID); (2) SOM (abnormal/normal); (3) pre-specified prognostic factors; (4) anxiety and depression scores at baseline; and, (5) resource utilization.

3. 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 (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 2006). 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) (Viceconte 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 et 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., 1997; Freeman and Guda, 2004). This risk has recently been reduced, but not eliminated, through the routine use of temporary pancreatic stenting (Jacob et al., 2001; Fogel et al., 2002;). 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., 1997; 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 (Khuroo et 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 1996) (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)

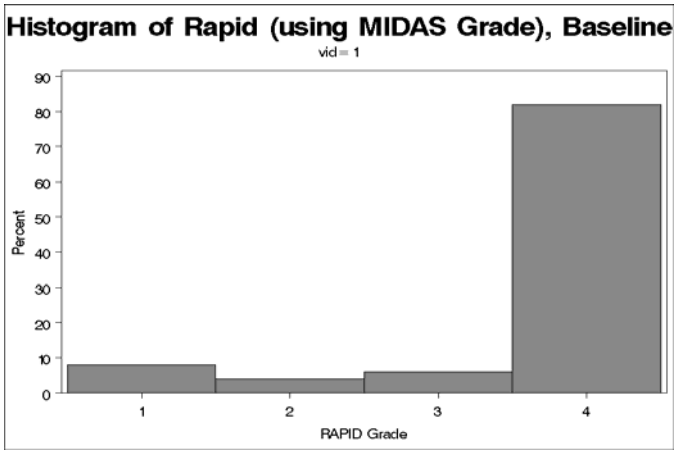
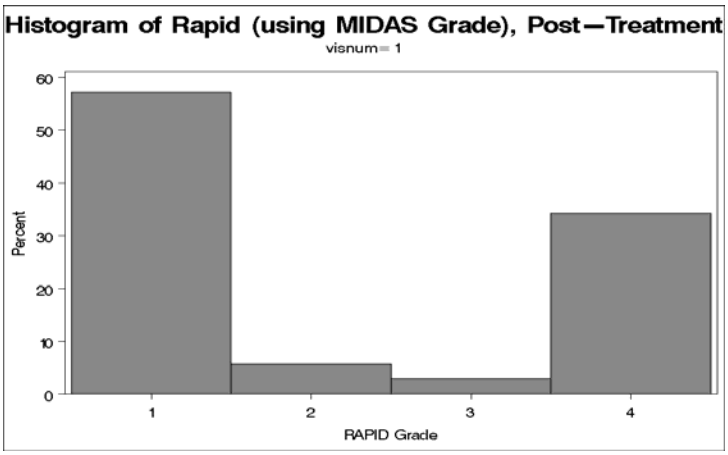


Figure 2: Post-Sphincterotomy RAPID Grade (n=70)



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 the "EPISOD" primary 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 (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, 1997; 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.
- The EPISOD2 study will include subjects who fit the inclusion criteria for the primary sham-controlled study ("EPISIOD"), but who decline randomization. It will provide additional imformation on the secondary end-points of the primary study, but also will show whether or not the subjects in EPISOD and EPISOD 2 are comparable. This will have important implications for the generalizability of the results of EPISOD.

4. STUDY PLAN

4.1. Study Design

This is a multi-center open-label study designed to document the outcomes and to characterize the patient population that undergo endoscopic sphincterotomy for the treatment of episodes of abdominal pain post-cholecystectomy. Subjects will include adults 18 to 65 years of age diagnosed with SOD III.

A maximum of 100 subjects, with no center entering more than 5 consecutive subjects per year during the enrollment period (Years 1-3), will be followed for 12 months post-randomization according to the Data Collection Schedule (below). Subjects completing the 12-month follow up without further endoscopic or surgical treatment, 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.

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

Same timeline as EPISOD study:

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

5. 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.
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. Able to speak, read, and write English.
14. Declined participation in the EPISOD Trial.
15. 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 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.

* *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. SUBJECT RECRUITMENT

Only subjects who decline participation in the EPISOD trial will be screened for EPISOD2, therefore all screening procedures for EPISOD2 will be the same procedures used in the main EPISOD trial.

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 eligibility, explain the study and conduct the research informed consent process.

7. INFORMED CONSENT PROCESS

All centers will use an IRB-approved consent document. 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.

8. ELIGIBILITY ASSESSMENT

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

9. SUBJECT ENROLLMENT

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

- Each Clinical Center will have **designated staff that** will perform enrollment procedures.

- **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.

- The computer will assign a unique subject 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.

10. STUDY PROCEDURES

10.1 Baseline Screening

An abbreviated list of activities and procedures conducted during baseline screening appears in the following table and each procedure is described in detail in Section 10.2-10.4 (below):

TABLE A: Baseline Screening & Evaluation Procedures
• Review of Medical History & Current Medications • Informed Consent • Results of Laboratory Tests, Imaging Results & Physical Examinations • Questionnaires: Modified FBDM, RAPID, RAPID START,SF-36, HADS, TRA, CSQ, BDI-II, RUF • MINI Interview • Physical Examination

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.

10.1.1 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 subjects and the original consent document will be filed in the subject record.

10.1.2. Medical History & Record Review: Medical history will include questions about current medications and 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 , herbal preparations, and nutritional supplements Results and reports from laboratory tests and/or other procedures will also be reviewed and documented to ensure eligibility with inclusion/exclusion criteria.

10.1.3. EPISOD Interviews & Surveys: A neuropsychiatric interview and other study instruments will be administered as part of baseline screening (see abbreviated list in

Table A above). Additional details describing the MINI interview and all other instruments are outlined in Section 11 of this protocol.

- MINI Interview
- Modified Rome III FBDM
- Rome III (FGD)
- RAPID START
- RAPID
- SF-36
- Hospital Anxiety and Depression Scale (HADS)
- Trauma
- Coping Strategies
- Beck Depression Inventory (BDI-II)

Resource Utilization

To ensure confidentiality, Coping & Trauma questionnaires will be placed in a sealed envelope as soon as completed by each subject.

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

10.1.5. Laboratory Tests

- **Blood Tests:** Blood samples will be obtained including a complete blood count (CBC), liver function tests (LFTs) and Amylase/Lipase tests.

- **Pregnancy Test:** Women who can possibly be pregnant, will have a blood serum pregnancy test performed since pregnant women, will not be allowed to take part in this study. (*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.

10.2 Non-Research Procedures – Standard of Care ERCP

10.2.1. Standard ERCP Medical Consent: All patients will review and sign a standard medical ERCP consent form (non-research) prior to the ERCP procedure which includes an outline of potential risks.

10.2.2. ERCP Procedure: Pre-procedure instructions, preparations and the procedure will be performed per standard clinical practice (non-research).

10.2.3. Recovery & Discharge: Post-procedure observation, recovery and discharge will be performed per standard clinical practice (non-research).

10.3 Research Packet: Each subject will receive a packet containing study contact information, a schedule of follow-up visits and hard copies of questionnaires to use as future reference during Months 1, 6, 9 and 12 telephone follow-up visits.

10.4 Follow-Up Assessments

Telephone Follow-Up (Months 1, 6, 9 & 12): Consented subjects who complete the Baseline Visit will receive follow-up telephone assessments at Months 1, 6, 9 & 12. RAPID and Resource Utilization Forms will be administered during the Month 9 and 12 follow-up phone calls by a central caller (not the primary coordinator). Telephone calls at Month 1 and 6 will be made by the primary coordinator and will capture data on adverse events and concomitant medications/procedures. The RAPID will not be administered during Month 1.

10.5 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.

11. ASSESSMENT INSTRUMENTS

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

RAPID: This instrument models the validated migraine scale, MIDAS, and measures the days lost in social, household and employment due to episodes of abdominal pain on a 3-month recall basis.

Modified Rome III 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.*

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.

SF-36: (Ware, 1987; www.sf-36.org/tools). The SF-36 is a comprehensive 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).

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.

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.

Coping Strategies 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.

Trauma Questionnaire – Short Form (TRA): 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.

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 approximately10 minutes to complete, and requires a fifth – sixth grade reading age to adequately understand the questions.

Economic Resource Utilization Forms: Resource utilization data in the form of answers to survey questions will be collected on separate telephone-administered case report forms (CRFs) to capture information on hospitalizations, physician/professional visits, employment information, and personal patient costs as outlined in the table above.

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

12. DISCONTINUATION OF PARTICIPATION

12.1 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, it will be documented in the End of Study case report form.

12.2 Subject Removal from Study

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

- Significant protocol violation, either on the part of the subject or Investigator.
- A procedural complication, which would interfere with the subject's continued participation.
- Refusal of the subject and/or the legal guardian to remain in the study (i.e. consent withdrawal).
- If the physician or sponsor believes it is in the subject's best interest to discontinue participation in the study.
- Administrative reasons, e.g., sponsor termination of the study.

12.3 Procedure for Discontinuation

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

(1) Adverse event assessment.
(2) Attempt to perform final follow-up evaluations.
(3) Complete the End-of-Study form, including an explanation of why the subject is withdrawing or withdrawn.

12.4. 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.

12.5. Re-entering the Study

If a subject who has withdrawn from the study voluntarily expresses interest in returning to complete the study, the subject cannot be re-entered.

12.6. Subject Transfers

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

13. OUTCOMES

This study is designed to gather pertinent descriptive information on the overall SOD III patient population. In addition to assessing the success rate based on the RAPID grade in subjects that undergo treatment for their episodes of pain, Secondary outcomes include (1) the RAPID score; (2) SOM results; (3) prognostic factors on the primary outcome; (4) anxiety and depression scores; and, (5) resource utilization.

14. DATA MANAGEMENT

14.1. 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.

14.2. 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.

14.3. Data Security and Confidentiality

During the course of the trial, user access to the files with Subject identifiers and files with study outcomes will be restricted to **Designated Study 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.

15. STATISTICAL CONSIDERATIONS

15.1. Statistical Analyses

15.1.1. Interim Analysis

There will not be an interim analysis on the EPISOD2 data.

15.1.2. Final Analysis

We are most interested in comparing the two cohorts, EPISOD and EPISOD2, in terms of their pre-procedure RAPID scores/grades, anxiety and depression levels, presence of irritable bowel symptoms, and any economic influences that may cause bias. These comparisons will be primarily descriptive and will aid in the generalizability of the findings from the EPISOD study. Two-sided 95% confidence intervals will be constructed and hypothesis tests will be conducted at an alpha level of 0.05.

15.1.3 Missing Data

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 to determine the reason for missing data. 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.

16. ADVERSE EVENTS

16.1. Definitions

16.1.1. Adverse Event (AE): 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.

16.1.2. Serious Adverse Event (SAE): 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.

16.1.3. Life-Threatening Adverse Event: Any adverse 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 which had it occurred in a more severe form, might have caused death.

16.2. Classification of Adverse Events

For the EPISOD2 Trial, adverse events that are classified as serious adverse events OR that increase risk(s) for participants, cause a change in the study design, or have higher prevalence than expected must be reported as outlined in the following section. These events will be classified as detailed in the EPISOD Manual of Procedures.

16.3. Obligations of Investigator

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 an event has been classified as a serious adverse event (SAE), the reporting procedures outlined in the next section will be followed.**

16.4. Reporting Procedures

WebDCU™: All ERCP related adverse event CRFs must be submitted via WebDCU™. These events will not be reviewed by a medical monitor since EPISOD2 is an observational study (minimal risk) and clinical interventions are not performed on study participants. However, this data will be reviewed by the EPISOD2 Executive Committee and subsequently reported to the EPISOD/EPISOD2 DSMB in periodic reports.

Institutional Review Board (IRB): Each site PI is responsible for reporting SAEs (including follow-up information) to the local IRB in accordance with local institutional requirements.

Follow-up Reporting: Each site PI is responsible for collecting follow-up data at Months 1, 6, 9 and 12 as outlined in the Data Collection Schedule (Section 10.5). All SAE information collected during these follow up calls will be submitted via electronic CRFs at WebDCU™.

16.5. Site IRB's

Site IRB's are responsible for prompt reporting to appropriate institutional officials, any supporting Agency or Department Heads and OHRP any unanticipated problems involving risks to subjects or others during participation in the EPISOD2 trial; any serious or continuing noncompliance with 45 CFR 46 or the requirements or determinations of the IRB; and any suspension or termination of IRB approval of the EPISOD2 trial at a participating site.

17. REGULATORY AND ETHICAL OBLIGATIONS

17.1. 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.

17.2. 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.

17.2.1. 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 local IRB for written approval.

17.2.2. 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 16 of this protocol.

17.2.3. Annual Renewal

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

17.3. 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. A list of the required regulatory documents is located in the current version of the Manual of Procedures on WebDCU™.

17.4. 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.

18. ADMINISTRATIVE AND LEGAL OBLIGATIONS

18.1. 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.

19. REFERENCES

Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory-II. 1996. San Antonio, TX: Psychological Corporation.

Bennett FJ, Piesse C, Palmer K, Badcock CA, Tennant CC, Kellow JE. Functional gastrointestinal disorders: psychological, social, and somatic features. Gut. 1998;42(3):414-20

Behar J, Corazziari E, Guelrud M, Hogan W, Sherman S, Toouli J. Functional Gallbladder and Sphin cter of Oddi Disorders. Gartoenterology 2006; 130:1498-1509

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

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.

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.

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

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.

Carlsson AM, Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analog scale. Pain 1983; 16: 87.

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.

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.

Corazziari E, Shaffer EA, Hogan W, Sherman S, Toouli J. Functional disorders of the biliary tract and pancreas. Gut 1999; 45:48-54.

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.

Cotton PB. ERCP is most dangerous for people who need it least. Gastrointest Endosc 2001; 54(4):535-6.

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.

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.

Deviere J et al., Nonresorbable copolymer implantation for gastroesophageal reflux disease: a randomized sham-controlled multicenter trial.. Gastroenterology. 2005 Mar;128(3):532-40.

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.

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.

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.

Drossman DA. The functional gastrointestinal disorders and the Rome II process. Gut 2006; 130: 1377-1390

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.

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.

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.

Farrar JT. What is clinically meaningful: outcome measures in pain clinical trials. Clin J Pain 2000; 16:S106-12.

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.

Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. Gastrointest Endosc 2004; 59(7):845-64.

Freeman ML, Nelson DB, Sherman S, et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med 1996; 335:909-18.

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.

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.

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.

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

Guy W. Clinical Global Impressions. New clinical drug evaluation unit (ECDEU) assessment manual for psychopharmacology. Washington, DC.1976; 218-222

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

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.

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.

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.

Hogan WJ, Geenen JE. Biliary dyskinesia. Endoscopy. 20 Suppl 1:179-83, 1988

Hogan W, Sherman S, Pasricha P, Carr-Locke DL. Sphincter of Oddi manometry. Gastrointest Endosc 1997; 45:342-8.

Hogan WJ. Hepatobiliary scintigraphy as the diagnostic test for sphincter of Oddi dysfunction: pan the scan? Am J Gastroenterol 2002; 97(6):1288-91.

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.

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

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.

Jones MP, Maganti K. Symptoms, gastric function, and psychosocial factors in functional dyspepsia J Clin Gastroenterol. 2004;38(10):866-72

Kalloo AN, Pasricha PJ. Therapy of sphincter of Oddi dysfunction. Gastrointestinal Endoscopy Clinics of North America. 6(1):117-25, 1996

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.

Katz J, Melzack R. Measurement of pain. Surg Clin North Am 1999; 79(2):231-52.

Keefe FJ, Williams DA. A comparison of coping strategies in chronic pain patients in different age groups. J Gerontol 1990; 45:P 161–5

Kellow JE. Sphincter of Oddi dysfunction type III: another manifestation of visceral hyperalgesia? Gastroenterology 1999; 116(4):996-1000.

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

Koloski NA, Talley NJ, Boyce PM, Epidemiology and health care seeking in the functional GI disorders: a population-based study. Am J Gastroenterol. 2002;97(9):2290-9

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.

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.

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.

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.

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.

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.

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

Madura JA, Madura JA II, Sherman S, Lehman GA. Surgical sphincteroplasty in 446 patients. Arch Surg 2005; 140:504-512.

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.

Mayer EA, Craske M, Naliboff BD. Depression, anxiety, and the gastrointestinal system. J Clin Psychiatry. 2001;62 Suppl 8:28-36;

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

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.

Mourits MP, van Kempen-Harteveld ML, Garcia MB, Koppeschaar HPF, Tick L, Terwee CB. Lancet 2000; 355:1505-9.

Okolo P, Sherman S, Lehman GA, Lovett e. Psychometric profiles of patients with sphincter of Oddi dysfunction. Gastrointest Endosc. 1994; 40:P119.

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.

Pasricha PJ, Miskovsky EP, Kalloo AN. Intrasphincteric injection of botulinum toxin for suspected sphincter of Oddi dysfunction. Gut 1994; 35:1319-21.

Pasricha PJ. There is no role for ERCP in unexplained abdominal pain of pancreatico-biliary origin. Gastrointest Endosc 2002; 56(6) Supplement:S267-72.

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.
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.

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.

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.

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.

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.

Sand J, Tainio H, Nordback I. Peptidergic innervation of human sphincter of Oddi. Dig Dis Sci. 1994;39(2):293-300.

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.

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.

Sherman S, Lehman GA. Sphincter of Oddi dysfunction: diagnosis and treatment. J Pancreas 2001; 2(6):382-400.

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.

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.

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.

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

Thune A, Scicchitano J, Roberts-Thomson I, Toouli J. Reproducibility of endoscopic sphincter of Oddi manometry. Dig Dis Sci 1991; 36(10):1401-5.

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.

Topazian M, Hong-Curtis J, Li J, Wells C. Predictors of outcome in post-cholecystectomy pain. Gastrointestinal Endoscopy 57(5): AB201, 2003.

Varadarajulu S., and RH Hawes. Key issues in sphincter of Oddi dysfunction. Gastrointest Endoscopy Clin N Am. 13 : 671-694, 2003.

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.

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.

Von Korff M, Ormal J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. Pain 1992; 50:133-49.

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

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.

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.

Ware JE. Standards for validating health measures: definition and content. J Chron Dis; 40:473-80, 1987.

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

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.

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