Evaluating **P**redictors & **I**nterventions in **S**phincter of **O**ddi **D**ysfunction:

EPISOD 3A Long Term Follow-Up Study

STUDY GROUP CHAIR

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Supported by:

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

Investigator's Agreement

I have read the attached clinical protocol titled "Evaluating Predictors & Interventions in Sphincter of Oddi Dysfunction: EPISOD 3 "A Long Term Follow-Up Study". Version 5 Dated September 3, 2014, 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

_____ _____

Signature of Co-Principal Investigator Date

(When applicable)

_____

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: EPISOD 3 "A Long Term Follow-Up Study"
Acronym	EPISOD 3
Clinical Trial Phase	Phase III
Study Sites	Medical University of South Carolina
Study Period	Planned Enrollment Period: 2 years Planned Duration of the Study: 4 years
Study Population	SOD III Patients who have completed the EPISOD or EPISOD 2 Trial
Primary Study Objective	To evaluate the long term effects of the treatment
Secondary Study Objective	To evaluate the stability of symptoms due to other functional gastrointestinal disorders (such as irritable bowel syndrome)
Study Design	Subjects who have previously been randomized into the EPISOD trial or enrolled into the EPISOD 2 trial will be asked to participate in follow up telephone contacts every 6 months for a maximum of four years after the completion of their initial trial period.
Sample Size	A total of 214 subjects will have been randomized into the EPISOD trial, while 72 subjects will have been enrolled into the EPISOD 2 trial; therefore approximately 286 subjects will be asked to participate in the EPISOD 3 trial
Inclusion Criteria	Subjects who have completed visit 12 of the EPISOD or EPISOD 2 trial
Exclusion Criteria	Subjects who have not completed the 12 month telephone follow-up visits for the EPISOD or EPISOD 2 trial.
Primary Outcome Measures	The goal is to characterize the population and determine the durability of treatment
Statistical Analysis for Primary Outcome Measures	Descriptive statistics including point estimates and 95% confidence intervals will be generated for all collected outcomes and presented by the EPISOD treatment arms (sham versus sphincterotomy).

2.0 OBJECTIVES

2.1 **Primary Goal**

To evaluate the long term effects of the treatment. The seminal but small randomized study of SOD type II subjects by Geenen and Hogan (1) had a follow-up period of 4 years. A total of 169 subjects in 8 other cohort studies of treatment of sphincter dysfunction had follow-up periods ranged from 15-57.6 months (2). Few studies give data on the number followed for more than one year, let alone 5 years. A study of different sphincter treatments in 313 subjects with SOD (of all types), showed that most treatment failures (measured by re-interventions) occurred within 12 months, but a significant number at a later date, especially those who underwent both biliary and pancreatic sphincterotomies (3).

2.2 **Secondary Goal**

To evaluate the stability of symptoms due to other functional GI disorders (such as IBS). The Rome process categorizes the many different functional digestive disorders based on clinical criteria that have been refined over 10 years. There are few data to show whether the symptom complexes are stable, i.e. that patients remain in the same category or sub-set over time. One study in patients with Irritable Bowel Syndrome showed a change in categorization in 25-50% (4). A detailed literature review of temporal patterns in Irritable Bowel Syndrome called for more prospective studies of the clinical course (5), a call echoed in the recent Rome III publication (6). No such studies have been reported looking at the fluctuation in symptoms of functional biliary and pancreatic disorders. The proposed study would allow also a longer

period in which to evaluate any relationship between symptom severity and any changes in psychiatric status.

3.0 BACKGROUND AND RATIONALE

The **EPISOD** study (Evaluating Predictors of Interventions in Sphincter of Oddi Dysfunction) is funded by NIDDK (DK074739-02), and recruitment started on August 5th 2008. Patients with SOD III as defined by Rome III clinical criteria were screened to show that they have no significant endoscopic, imaging, or laboratory abnormalities, and to have had appropriate trials of medical treatment. After informed consent, they underwent ERCP with biliary and pancreatic manometry. They were then randomized to sphincterotomy or sham, regardless of the manometry results (2:1 sphincterotomy versus sham). Those patients randomized to the sphincterotomy arm and who had raised pancreatic sphincter pressures were randomized again to biliary or to biliary and pancreatic sphincterotomy. All subjects got a small temporary pancreatic stent. Patients, caregivers, and research coordinators were blinded to the treatment allocation. Success was defined by substantial reduction in pain burden at 1 year (without any repeat intervention).

A total of 214 subjects were enrolled in 8 centers in the USA.

EPISOD 2 is a subsidiary study that includes subjects eligible for EPISOD, but who decline randomization. They are documented and followed in a similar fashion. A total of 72 patients were enrolled.

The results of the EPISOD and EPISOD 2 trials were published recently (7).

4.0 STUDY PLAN

Subjects that have been randomized into the EPISOD trial, or enrolled into the EPISOD2 trial will be recruited by the central caller coordinator at the coordinating center. Upon agreeing to participate in and consenting over the phone for this long term follow-up study, subjects will be contacted every 6 months for a maximum period of 4 years. . All telephone visits will be performed by the central coordinating center's coordinator. During this time, a selection of questionnaires will be administered via a telephone call with the subjects. Each of these questionnaires will be familiar to the subjects as they have been used in the EPISOD and EPISOD 2 trials.

5.0 ELIGIBILITY CRITERIA

Subjects must have completed the one year follow-up period for EPISOD and EPISOD 2 to be considered eligible for the EPISOD 3 trial.

6.0 STUDY PROCEDURES

6.1 Informed consent will be obtained through an IRB approved telephone consent script before any study related procedures/questionnaires will be performed. The Clinical Coordinating Center Investigators or their designated staff will discuss the study and give the subject opportunities to ask questions about the study. A copy of the dated telephone informed consent will be filed with the subject record.

6.2 All follow up telephone visit questionnaires will be performed by a central caller. This same system was used in the EPISOD and EPISOD2 trials for standardization of a primary indicator for the study. Participating centers in the EPISOD and EPISOD2 trials have obtained their individual IRB's approval for this follow-up.

6.3 Questionnaires to be utilized during the study;

6.3.a. **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 (8).

6.3.b. **Hospital Anxiety and Depression Scale (HADS):** (9). 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.

If the depression HADS score is ≥20 or increases by 50% or more from the subject's last HADS depression subscale score for EPISOD-1 or 2 study phase, when the score is 10 or greater, study staff will recommend for participant(s) to contact a mental health professional or his/her treating PCP for further assessment and/or treatment.

6.3.c **Resource Utilization Follow—up Questionnaire:** 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 Standard Follow-up CRF (6 month recall) is two pages, and captures information on hosptializations, physician/professional visits, employment information, and personal costs

6.3.d. **SF-36:** (10). 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 by the US Public Health Service's Panel on Cost-Effectiveness in Health and Medicine

6.3.e. **ROME III Diagnostic Module:** 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.

6.3.f. **Coping Questionnaire-Catastrophizing Subscale (CSQ-Catastrophizing):** (11,12) 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.

6.3.g. **Patients Global Impression of Change (PGIC): (13,14)**. This questionnaire has been validated in other disease states and designed to measure overall improvement relative to a baseline. 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.

6.3.h. **Pain Questionnaire:** The purpose of this instrument is to better understand how the subject defines an episode of pain.

6.4 Data Collection Schedule

6.4.a. Every 6 months: RAPID, HADS, PGIC, RUQ

6.4.b. Every 12 months: ROME III Modular Questionnaire, Coping Questionnaire at Months 36 and 48, and SF-36.

7.0 DATA MANAGEMENT

Data Management for the EPISOD 3 trial will be conducted by the current EPISOD Statistical and Data Management Center which is housed in the Department of Public Health Sciences Data Coordination Unit (DCU) at the Medical University of South Carolina. All activities will be conducted in coordination with the EPISOD Clinical Coordinating Center. The study data will be managed (including data queries) by the SDMC using the WebDCU™ system. This electronic data management system currently is used for several federally-funded multicenter studies including EPISOD and EPISOD2. This user-friendly web-based database system, developed and validated by the SDMC, will be used for subject enrollment, data entry, data validation, subject tracking, user customizable report generation and secure data transfer. In addition to the study database, the SDMC will provide the coordinating center staff access (via password) to a standard set of web-enabled tools, including subject visit calendar, subject accrual status, case report form completion status, and outstanding DCR status. Furthermore, all approved study materials, such as the protocol, informed consent template and manual of procedures, will be housed on the website to ensure that the coordinating center always has access to the most current trial documents.

8.0 ADVERSE EVENTS

8.1 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. As this study is a naturalistic follow up, non-serious adverse events will not be tracked.

8.2 Serious Adverse Event (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.

8.3 Serious Adverse Event Reporting Procedures. Serious Adverse Events will be reported online via the WebDCU™. Serious Adverse Events must be reported to the clinical coordinating center within 24 hours of notification of the event.

9.0 REGULATORY AND ETHICAL OBLIGATIONS

9.1 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.

The original signed telephone consent form 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. The IRB approved telephone informed consent will be signed and dated by the individual obtaining that consent.

9.2 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.

9.2.a. 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.

9.2.b. 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 8.0 of this protocol.

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

10.0 PRE-STUDY DOCUMENTATION REQUIREMENTS

The Principal Investigator at the EPISOD coordinating center is responsible for all required regulatory documents PRIOR to recruitment for the EPISOD 3 trial. These documents are located in the current version of the Manual of Procedures on WebDCU™.

11.0 SUBJECT CONFIDENTIALITY

The Principal Investigator at the EPISOD coordinating center must ensure that subject confidentiality is maintained. Enrolled subjects will be identified on any study documentation only by their initials and study identification number generated by WebDCU™.

12.0 ADMINISTRATION AND LEGAL OBLIGATIONS

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 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.

13.0 STUDY ORGANIZATION

13.1 The study will be conducted by the Principal investigator (Peter Cotton), Co-investigators (Patrick Mauldin and Olga Brawman-Mintzer), Program manager (April Wood) and Consultant (Douglas Drossman), in collaboration with the Statistical and Data Management Center.

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

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