Document:
Study Protocol and Statistical Analysis Plan

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AnX Navicam Magnetically Controlled Capsule Endoscopy Feasibility Study in Gastric Motility

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AnX Navicam Magnetically Controlled Capsule Endoscopy Feasibility Study in Gastric Motility

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Introduction

Gastroparesis and functional dyspepsia are commonly diagnosed upper gastrointestinal (GI) disorders. The prevalence of gastroparesis and functional dyspepsia are estimated to be 1.5-3% and 10-30%, respectively.[1,2] Both can present with abdominal pain, dyspepsia, nausea, emesis, or early satiety. Gastroparesis is a syndrome defined as delayed gastric emptying. Functional dyspepsia is a symptom-based diagnosis in which the pathophysiology is multifactorial. Delayed gastric emptying is present in 25-35% of patients with functional dyspepsia.[2] Other pathophysiologic mechanisms include impaired gastric accommodation, gastroduodenal dysmotility, gastroduodenal hypersensitivity, and duodenal inflammation. A major barrier in the management of these disorders is the lack of a biologic marker that is highly correlated with symptoms and predicts response to treatment. Characterizing gastric motility may yield potential actionable biomarkers for gastroparesis and functional dyspepsia, however all currently available methods for evaluation of gastric motility have significant drawbacks. The gold standard method – nuclear medicine gastric emptying study (GES) - exposes patients to radiation, is time consuming (2-4 hours), and results do not consistently correlate with patient symptoms. The wireless motility capsule and Carbon^{13} breath testing are used commercially but both lack sensitivity and specificity when compared to GES. Other measures like gastric manometry, gastric barostat, electrogastrography, or ultrasound are cumbersome and have not become widely available in clinical practice. Furthermore, none of these available methods have the ability to visualize gastric peristalsis in real-time, or assess the contribution (or lack of contribution) of different anatomic sections of the stomach to motility.

We propose the Navicam magnetically controlled capsule endoscopy (MCCE) system as a potential new method of evaluating gastric motility disorders. The MCCE is FDA approved for visualization of the stomach. The ability to visualize gastric peristalsis in real time, without interference from an endoscope, has never been demonstrated. The MCCE system could allow physicians to evaluate gastric motility with a test that has clear advantages over the current methods: it is fast, non-invasive, and has no radiation exposure, has artificial intelligence (AI) capabilities, while at the same time provides a visual assessment of the gastric anatomy.

Significant clinical implications

1) Evaluating for gastric motility disorders in patients presenting with abdominal pain, dyspepsia, nausea, vomiting, and/or early satiety
2) Establishing or ruling-out a diagnosis of gastroparesis or functional dyspepsia
3) Providing objective treatment response metrics in patients with gastroparesis or functional dyspepsia

a. After treatment with medications
b. After treatment with endoscopic interventions (ie G-POEM*)
c. After treatment with gastric pacemakers

*G-POEM = Gastric Per-Oral Endoscopic Myotomy

Innovation

Because this is a proven technology for mucosal tissue visualization but a novel application for functional gastroduodenal and motility disorders, the initial research will be an information gathering feasibility study. Future studies will build on the information learned.

Specific Aims

1. Visualize and compare the patterns of gastric peristalsis in different anatomic sections of the stomach in the fasting state in healthy controls, patients with gastroparesis, patients with functional dyspepsia, and patients who have undergone G-POEM
    a. Compare patterns with healthy and disease states
2. Visualize and compare the mechanisms of particle mixing (using luminal transit markers*) in different anatomic sections of the stomach in the fasting state in healthy controls, patients with gastroparesis, patients with functional dyspepsia, and patients who have undergone G-POEM
    a. Compare patterns with healthy and disease states
3. Visualize and compare the patterns of gastric peristalsis in different anatomic sections of the stomach with food stimulation in healthy controls, patients with gastroparesis, patients with functional dyspepsia, and patients who have undergone G-POEM
    a. Compare patterns with healthy and disease states
4. Visual and compare patterns of gastric peristalsis in different anatomic sections of the stomach during moments of patient discomfort in healthy controls, patients with gastroparesis, patients with functional dyspepsia, and patients who have undergone G-POEM
    a. Compare patterns with healthy and disease states

*Luminal transit markers = FDA approved IntraMarX markers

Study Design

Study Subjects and Recruitment:

In this pilot feasibility study, we plan to enroll 5 male and female adult healthy volunteers, 5 male and female patients with gastroparesis, 5 male and female patients with functional dyspepsia (epigastric pain syndrome and/or postprandial distress syndrome with or without gastric emptying delay), and 2 patients with gastroparesis who have undergone a G-POEM procedure. All study subjects will be 18 years or older. Gastroparesis, functional dyspepsia, and G-POEM patients will be recruited from the UCLA GI clinics and will need to meet the diagnostic criteria (see below). The healthy volunteers will be recruited from community advertisement and from the Center for Neurobiology of Stress and Resilience (CNSR) healthy volunteer database.

Inclusion Criteria:

Gastroparesis

1) Meets diagnostic criteria for gastroparesis[3]
    a. Evidence of delayed gastric emptying documented with a standard 2 hour or 4 hour gastric emptying scintigraphy exam
    b. Absence of mechanical obstruction
    c. Exhibits cardinal symptoms of early satiety, post-prandial fullness, nausea, vomiting, bloating, and upper abdominal pain
2) Gastrointestinal cardinal symptom index (GCSI)[4] score > 0 (i.e., the presence of at least mild severity of ≥1 of 3 symptoms of nausea/vomiting, postprandial fullness/early satiety, and/or bloating).

Functional Dyspepsia

1) Meets Rome IV diagnostic criteria for functional dyspepsia[2]
    a. Criteria fulfilled for the last 3 months with symptom onset at least six months prior to diagnosis
    b. No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at upper endoscopy)
    c. Meet criteria for Epigastric pain syndrome and/or Postprandial distress syndrome

        i. Epigastric Pain Syndrome
            1. At least 1 of the following symptoms at least 1 day per week
                a. Bothersome epigastric pain
                b. Bothersome epigastric burning
        ii. Postprandial Distress Syndrome
            1. At least 1 of the following symptoms at least 3 days per week
                a. Bothersome postprandial fullness
                b. Bothersome early satiation

G-POEM subjects

1) The G-POEM procedure must have been performed at least 4 weeks prior to screening.
2) GCSI[4] score is < 3 which correlates to mild or less symptom severity.

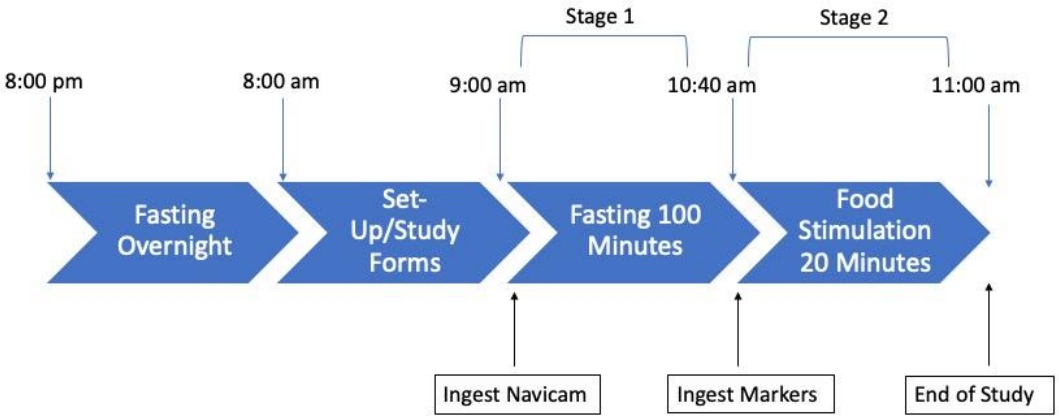
Exclusion Criteria:

1) Another active disorder or treatment which could explain or contribute to symptoms in the opinion of the Investigator (including but not limited to gastric malignancy, neurological disorder, or heavy doses of strong anticholinergics. "Heavy doses" means dose levels, that - in the investigator's judgment - could account for the participant's gastroparesis, functional dyspepsia, or epigastric pain syndrome.).
2) Gastrectomy, fundoplication, vagotomy, bariatric surgery, post-surgical cause of gastroparesis, or gastric stimulation device surgically implanted within the last year. Prior G-POEM procedure for gastroparesis is allowed for the group of post-G-POEM study subjects.
3) Dysphagia, swallowing disorder
4) Suspected bowel obstruction or perforation

5) Gastric or parenteral feeding within 4 weeks of screening
6) Pregnancy or nursing
7) History of an eating disorder within 2 years of screening
8) Recent history (within six months of screening) of Alcohol Use Disorder or Substance Use Disorder as defined in DSM-5.
9) Uncontrolled thyroid disease
10) Unstable cardiac, respiratory, hepatic or renal disease
11) Evidence of uncontrolled blood glucose (including HbA1C >9 or metabolic crisis in past 60 days).
12) Use of prohibited medication or medication with anti-nausea, antiemetic, neuromodulating, or prokinetic effect within 2 weeks of the screening visit EXCEPT when administered on a stable daily dosing schedule (stable for at least 1 month prior to the screening visit).
13) Use of as needed or daily opioids within the past 1 month.
14) Pyloric injection of neurotoxins (e.g. botulinum type A or B) within 3 months of the Screening visit.
15) Altered mental status (e.g., hepatic encephalopathy) that limits the ability to swallow a capsule
16) Expected to have Magnetic Resonance Imaging (MRI) examination within 30 days.
17) No reliable contact information – no phone, no permanent address.
18) Pacemaker or ICD
19) Inability to avoid using the bathroom for urination and/or bowel movements for the duration of the study.
20) Metal Implant (ie metal hip arthroplasty, surgical mesh, coronary or arterial stent)
21) Prior bowel surgery
22) Severe claustrophobia
23) Any other reason as determined by the Investigator which may lead to an unfavorable risk-benefit of study participation, may interfere with study compliance, or may confound study results.

Study Protocol:

Schematic Overview:



Detailed Protocol:

Prescreening will be via telephone.

Screening will be done with a video or in person visit where there will be discussion of the benefits and risks of the study, and eligible study subjects will sign informed consent and email scanned consent form to study team. Subjects will bring original signed copy on the day of the examination.

Pre-Exam

1) Patient should stop medications for 2 days prior to the exam that may affect gastric motility. This includes prokinetic agents (for example; metoclopramide, prucalopride) and medications that delay gastric emptying (e.g., antispasmodics, anticholinergics).
2) Patient should abstain from drinking barium as part of a medical test for 3 days prior to the exam
3) Eat a light dinner on the night prior to the study. Fast after dinner, except for clear liquids (no colored liquids).
    a. Patients with gastroparesis will be on a clear liquid diet for the entire day prior the procedure (then fasting completely after 8pm)
4) Patient to wear loose fitting clothes without metallic items (buttons, zippers, etc)

Day of Exam

5) 8am: arrive at UCLA CNSR examination room
6) 8 – 9:00am
    a. Bring original signed informed consent
    b. Complete questionnaires
        i. Rome IV functional dyspepsia questions[2]
        ii. Patient Assessment of Gastroparesis Cardinal Symptom Index (GCSI)[5]
        iii. Generic quality of life (SF-12)[6]

iv. Dyspepsia severity scale (DSS) (sum of the severity scores at every time point for fullness, epigastric pain, epigastric burning, nausea, and bloating, each on a scale of 0-4, 0= absent and 4=very severe).[7]
v. Hospital Anxiety and Depression Scale (HAD)[8]
vi. Medication list

c. Drink 40mg simethicone (standard, over the counter)
d. Drink up to 1 liter of water from 8 – 9am
e. Perform DSS
f. Get in postion for MCCE

7) 9:00am: Start of test.
8) 9:00am – 10:40am: **STAGE 1**: Observe gastric motility in the fasting state.
   a. ~ 50-55 minutes will be in quiescent state (phase I of Migrating Motor Complex)
      i. 10 minutes aimed at fundus
      ii. 5 minutes aimed at cardia (close up)
      iii. 10 minutes aimed at gastric body greater curvature
      iv. 5 minutes aimed at gastric body lesser curvature
      v. 5 minutes aimed at angularis (retroflexion) gastric body lesser curvature
      vi. 10 minutes aimed at antrum
      vii. 10 minutes aimed at pylorus (close up)
   b. ~ 30-35 minutes will be in irregular contractile activity (phase II of Migrating Motor Complex)
      i. 6 minutes aimed at pylorus (close up)
      ii. 6 minutes aimed at antrum
      iii. 3 minutes aimed at fundus
      iv. 3 minutes aimed at cardia
      v. 6 minutes aimed at gastric body greater curvature
      vi. 3 minutes aimed at gastric body lesser curvature
      vii. 3 minutes aimed at angularis (retroflexion)
   c. ~ 10-15 minutes will be in high-amplitude, rhythmic, peristaltic contraction (phase III of Migrating Motor Complex)
      i. 2 minutes aimed at pylorus (close up)
      ii. 3 minutes aimed at antrum
      iii. 1 minute aimed at angularis (retroflexion)
      iv. 1 minutes aimed at gastric body greater curvature
      v. 1 minute aimed at gastric body lesser curvature
      vi. 1 minute aimed at fundus
      vii. 1 minute aimed at cardia
   d. Note 1: 100 minutes is an maximum time for a patient to go from the beginning of phase I to the end of phase III of the MMC. The timing is likely to differ between patients, and may even differ between different periods of the Navicam examination within an individual patient. The operator performing the test will determine when there is a change of MMC phase and move to the next phase.
   e. Note 2: We will not know which phase of the MMC the patient will be in prior to the exam. Once the Navicam is deployed, the operator will visually determine the phase, and start the appropriate protocol. The primary goal is to observe phase III. Therefore, as soon as MMC III has been completed, we will move to the next part

of the exam. This means that some patients will not have a full exam of all three MMC phases during this first period (for example, if a patient is in MMC II when the Navicam is deployed and then progresses to MMC III, we will not view MMC I during this initial period).

9) 10:40 – 11:00: **STAGE 2-** Observe gastric motility and movement of luminal transit markers after a sham meal, i.e. chewing/spitting an appealing food item (ie fast food burger)
    a. Patient swallows 24 luminal transit markers
    b. Put patient on side
    c. Give patient hamburger, fries, and soda (or patient can bring own food) to chew and spit out
        i. 3 minutes aimed at fundus
        ii. 2 minutes aimed at cardia (close up)
        iii. 3 minutes aimed at gastric body greater curvature
        iv. 2 minutes aimed at gastric body lesser curvature
        v. 2 minutes aimed at angularis (retroflexion) gastric body lesser curvature
        vi. 3 minutes aimed at antrum
        vii. 3 minutes aimed at pylorus (close up)
        viii. 1 minute at fundus counting markers
        ix. 1 minute at antrum counting markers
10) 11:00am: Study End

Note: During the examination, the operator will follow the protocol as detailed above. If at any point during the exam, the patient describes abdominal discomfort (similar to their usual symptoms of dyspepsia or gastroparesis), the time of discomfort should be documented, and the dyspepsia severity scale should be filled out by the patient. If technically feasible, the operator should do a quick sweep of the stomach during the period of discomfort. (This can be omitted during phase III of MMC, in which the operator will already be doing a sweep of the stomach)

i. 1 minute aimed at fundus
ii. 1 minute aimed at cardia (close up)
iii. 1 minute aimed at gastric body greater curvature
iv. 1 minute aimed at gastric body lesser curvature
v. 1 minute aimed at angularis (retroflexion) gastric body lesser curvature
vi. 1 minute aimed at antrum
vii. 1 minute aimed at pylorus (close up)

<u>Video imaging assessment</u>

1) Operator to mark times of phase I, II, and III during Stage I of the study period
2) Operator to mark location of the different gastric segments with image capture.

<u>Main Outcome Measures</u>:

1) Frequency of contractions and direction (e.g., towards fundus or antrum). In Stage 1, this will be done during phase III of MMC. In Stage 2, these contractions will be measured after the sham meal.
2) Number and location of luminal transit markers in the antrum and fundus of the stomach and total in the stomach during Stage 2. The number of markers will be counted after the sham meal.
3) Largest diameter of the pylorus during phase I, II, and III of MMC during Stage 1 and after the sham meal in Stage 2.
4) Assess change (from baseline to after water is taken) in brightness as a function of depth and accommodation in the fundus using the fix light exposure mode. Total water intake will be recorded.
5) Dyspepsia Severity Scale symptom ratings at baseline (Stage 1) and during the study at timepoints with discomfort if present.
6) Procedure related adverse events.

Study Questionnaires and Definitions

GCSI[4]
3 subscales from the PAGI-SYM: nausea/vomiting, postprandial fullness/early satiety, and bloating.

Dyspepsia Severity Scale[7]
6 epigastric symptoms (fullness, bloating, nausea, epigastric pain, burning, and belching). Severity (0, absent to 4, very severe). Sum of the 6 epigastric symptoms will be calculated.

SF-12[6]
The 12-Item Short Form Health Survey (SF-12) is a validated short form of the original 36-Item Short-Form Health Survey (SF-36) used to measure health related quality of life.

MMC
Migrating Motor Complex. The MMC is the natural pattern of gastroduodenal peristalsis in the fasting state. There are three recurring phases. Phase I is a quiescent state, with little activity. Phase II has irregular contractions. Phase III is a coordinated movement of powerful contractions, intended to clear the gut; this has been called the "house-keeping" phase.

Sample size and statistical analysis
This is a pilot, feasibility trial in healthy human subjects, patients with gastroparesis without and without a prior G-POEM procedure, and patients with functional dyspepsia, with the main objective to test the feasibility of visualizing gastric motility and accommodation as a biologic marker of gastroparesis and functional dyspepsia. In addition, this feasibility study will estimate parameters such as mean and standard deviation which will be used in a sample size calculation for the full-scale trial. The sample size will be 5 subjects in each group of gastroparesis, functional dyspepsia and healthy controls. There will only be 2 gastroparesis patients s/p G-POEM procedure because this procedure is only reserved for patients who are refractory to medical management and has very limited insurance coverage so it is only infrequently performed. This procedure is performed at UCLA and we feel that we can study two patients

who meet the inclusion and exclusion criteria for this study. To account for potential screen failures (n=3) or dropouts (n=2), we will plan on screening 22 subjects. As per sample size recommendations for pilot studies, a total sample size of 22 completed subjects should be sufficient to provide initial feasibility and safety.[9]

Between group differences at baseline (Stage 1) as well as after ingestion of markers and the sham meal (Stage 2) will be measured using ANOVA and Chi-Square tests. Paired T-Tests and repeated measures ANOVA will be used to analyze the changes in continuous outcome variables and Chi-Square tests will be used for categorical outcome variables in Stage 2 compared to Stage 1. We will test the hypothesis that the true mean difference between the groups and time points is 0. A separate model will be fitted for each of these outcomes. Specifically, for outcome #1, we will compare the frequency of gastric contractions between the groups at Stages 1 and 2. The frequency of contractions after ingestion of luminal markers and sham meal (Stage 2) will be compared to the baseline (Stage 1, phase III of MMC), using paired T-tests, with the frequency as a dependent variable and time as an independent variable. Additionally, the direction of contractions (e.g., towards fundus or antrum) between groups and at baseline vs Stage 2 will be tested using Chi-Square test. For outcome #2, we will count the number of luminal transit markers that are remaining in the antrum, remaining in the fundus, and in the entire stomach in Stage 2. For outcome #3, paired T-tests will be used to test the differences between the largest diameter of the pylorus during phase I, II, and III of MMC during Stage 1 and 2. For outcome #4, we will compare the change (from baseline to after water is taken) in brightness as a function of depth and accommodation in the fundus between groups. For outcome #5, paired T-Tests will be used to compare Dyspepsia Severity Scale symptom ratings at baseline (Stage 1) and during the study (Stage 2). and ANOVA will be performed to compare the severity between groups. Correction for multiple comparisons for exploratory studies is not recommended.[10,11] This is a pilot, feasibility study and is intended to provide specific information to plan for subsequent larger studies and therefore may not need correction for multiple comparisons.

Potential Risks and Benefits

Potential Risks:

We have considered a variety of potential risks to participants including cognitive, affective, physical, legal/confidentiality and economic risks. The NaviCam MCCE is manufactured by AnX Robotica has been recently cleared by the FDA through the de-novo process to confirm its safety and effectiveness profile.

Since its introduction to the Chinese market after being approved by the Chinese Food and Drug Agency (CFD) in 2012, the NaviCam MCCE was subject to a series of clinical studies. In a review of 29 capsule studies including 7612 gastric capsule procedures with the NaviCam in mostly asymptomatic adult subjects, but they also included children, older adults, and patients with Crohn's disease. The rate of adverse events associated with the system has been found to be extremely low. The incidence of adverse events were: abdominal pain 0.03% (n=2), bloating 0.16% (n=12), nausea 0.20% (n=15), vomiting 0.01% (n=1), other (headaches, foreign body sensation) 0.03% (n=2), and capsule retention 0.11% (n=8).

The physical risks associated with the NaviCam MCCE are generally related to potential non-natural excretion. There is a small risk that the capsule could become stuck in the stomach or small intestine. Based on published and unpublished data of other types of capsule endoscopes, retained capsules have persisted in the GI tract for periods for many years without adverse event. In fact, a large retrospective review by Cheifetz, et al. found that a retained capsule is often asymptomatic or leads to a diagnosis.[12] Furthermore, the device is made of biocompatible materials and its internal parts are non-toxic. The incidence of capsule retention has been reported to be less than 1% but this figure may be higher in Crohn's disease or other conditions. The rate of surgical/endoscopic removal was noted to be 0.75%.[13]

Patients who are at increased risk of capsule retention are not appropriate study subjects including people with swallowing disorders or with known or suspected gastrointestinal obstructions, strictures or fistulas. However, in gastroparesis, the MCCE may pass through the stomach more slowly. Any patient with dysphagia will be excluded because a retained capsule in the esophagus is at risk of aspiration.

Study subjects will be advised not to have an MRI for 30 days. For patients who are unsure whether they excreted the MCCE, the patient can return to CNSR and the device scanner will determine if the MCC is still within the body of the subject.

In order to maximize safety for all study subjects, only consented and enrolled subjects will be administered the MCCE under the supervision of a physician and a subinvestigator/ trained research associate responsible to the PI. In addition, the MCC will be stored in a secure, limited access area. Product accountability log must include the protocol number, investigative site name, product name, medical units (i.e., capsules), serial number and subject ID number.

We anticipate low cognitive risk to participants. Diagnosis of source of abdominal symptoms is presumably one of the reasons the patient presented for emergency care. We do not anticipate an affective risk to participants. Some participants may be bothered by the knowledge that the device will pass naturally and may take several days to be excreted.

We believe the study poses a low privacy risk to subjects as all data will be encrypted and no PHI will be stored with data. Data will be stored in a Microsoft Access database which is the platform used by CNSR for their clinical research studies for many years.

Finally, the study has a low economic risk since the device and the interpretation of the device are not being billed to the subject or his/her insurance company. AnX Robotica, the manufacturer of the NaviCam has agreed to cover the cost of medical care and treatment for research injuries sustained by subjects enrolled in the study in accordance with the terms of the Clinical Trial Agreement and there is no economic risk expected as a result of unanticipated complications of the device as these will be covered by AnX Robotica, per the final negotiated terms in the Clinical Trial Agreement (currently under negotiation).

Major adverse events that occur will be reported directly to the principal investigator and overall study coordinator within 24 hours. Minor adverse events include inability to tolerate the MCC capsule, discomfort swallowing capsule, issues regarding video capture, issues regarding video transmission, erroneous video interpretation that has no significant impact on clinical care, protocol deviations, reactions to medication (promotility agent), delays in endoscopy interpretation, delays in EGD and others. All minor adverse events will be shared with the entire research team at regularly scheduled monthly calls or sooner at the PI's discretion.

Any major adverse events that occur will be reported directly to the principal investigator who will be available to study subjects 24 hours a day. Severe adverse events will be reported to the entire research team, the sponsor, and the UCLA IRB within 24 hours. Updates will be provided after a full investigation is completed. SAE's will also be reported to the FDA. Potential major adverse events include missed high-risk lesions, delayed definitive care, patients who are discharged from medical care prematurely and experience a major outcome (see below), capsule retention in the small bowel, and any serious outcome that may be related to study protocol.

Potential Benefits:
Immediate potential benefits include a focused effort by the research team to visualize the stomach for all subjects and help ensure appropriate follow-up. Long-term potential benefits include more effective and efficient management of a variety of conditions that are common in the population.

Data Entry System
For this protocol, Microsoft Access database will be used for data entry screens corresponding to the study forms that will be developed and maintained by CNSR. Clinical center staff will enter de-identified data into the subject database.

Assessment of Safety

Unanticipated Adverse Events:
An unanticipated adverse event is an effect on health or safety caused by, or associated with, a device, if that effect or problem was not previously identified in nature, severity, or degree of incidence in the protocol, or any other unanticipated problem associated with a device that relates to the rights, safety, or welfare of subjects in the clinical study.

Assessment of Adverse Events:
All adverse events will be graded for severity as follows:

Mild: Sign or symptom, usually transient, requiring no special treatment and generally not interfering with usual activities.

Moderate: Sign or symptom, which may be ameliorated by simple therapeutic measures; yet, may interfere with usual activity.

Severe: Sign or symptom that are intense or debilitating and that interfere with usual activities. Recovery is usually aided by therapeutic measures.

The relationship of the adverse event to the study device is defined as follows:

Probably related: Follows a reasonable temporal sequence from study device use delivery/retrieval and cannot be reasonably explained by known characteristics of the subject's clinical data.

Possibly related: Follows a reasonable temporal sequence from study device delivery/retrieval but could have been produced by the subject's clinical state regardless of the study device.

Not related: No relationship to study device activation is perceived.

Serious Adverse Events:
Adverse events will be reported within 24 hours to the Study PI, the local IRB and the sponsor.

Additional procedures are warranted for cases of serious adverse events which is defined by the FDA as an adverse event that:
a) Led to death,
b) Led to serious deterioration in the health of the subject, that either resulted in:
1) A life-threatening illness or injury, or
2) A permanent impairment of a body structure or a body function, or
3) In-patient or prolonged hospitalization, or
4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c) Led to fetal distress, fetal death or a congenital abnormality or birth defect

Reporting Procedures:
All device related serious adverse events should be reported to the PI, Sponsor, UCLA IRB, and FDA.

Unanticipated adverse events should be reported to the PI, Sponsor, and UCLA IRB in a timely manner.

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