TITLE: Evaluation of Ability to Detect Bowel Gas during Laparoscopic Right Colectomy with Intracorporeal Anastomosis

IRB Protocol #: 20-10022823
NCT#:NCT04964297
Version Date: 06/03/2024
Funding Source(s): Sentire Medical Systems, Inc., USA

TITLE: Evaluation of Ability to Detect Bowel Gas during Laparoscopic Right Colectomy with Intracorporeal Anastomosis

IRB Protocol #: **20-10022823**
IND/IDE #: (if applicable)
Version Date: 06/03/2024
Funding Source(s): Sentire Medical Systems, Inc., USA

Principal Investigator: Mehraneh Dorna Jafari, MD
525 East 68th Street, K-802A
New York, NY 10065
646-962 2342

Co-Investigators*:*

Jeffrey Milsom, MD
Professor of Surgery
525 East 68th Street, K-802
New York, NY 10065
646 962 2270

Parul J .Shukla, MD
Professor of Surgery
525 East 68th Street, K-802
New York, NY 10065
646 962 2270

Kelly Garrett, MD
Associate Professor of Clinical Surgery
525 East 68th Street, K-802
New York, NY 10065
646 962 2270

Heather Yeo, MD
Associate Professor of Surgery
525 East 68th Street, K-802
New York, NY 10065
646 962 2270

Lea Lowenfeld, MD
Assistant Professor of Surgery
525 East 68th Street, K-802
New York, NY 10065
646 962 2270

Koiana Trencheva, BSN, M.S.
Research Associate
525 East 68th Street, K-802B
New York, NY 10065
646-962 2342

kivanova@med.cornell.edu

Elain Darling, CNP OCN Nurse Practitioner
525 East 68th Street, K-802
New York, NY 10065
646-962-3037

Wooyon Choi Research Assistant
525 East 68th Street, K-801
New York, NY 10065
646-962 2789
woc4001@med.cornell.edu

Kristina Hosi. *Clinical Trials Program Manager, Department of Surgery*
Tel: 646.962.9417
krh7011@med.cornell.edu

Statistician: *Paul J. Christos, Dr. P.H., M.S.*
Director, Research Design and Biostatistics Core,
Clinical and Translational Science Center
Division of Biostatistics and Epidemiology
Department of Healthcare Policy and Research
Weill Cornell Medical College
pac2001@med.cornell.edu

Medical Monitor: N/A

Participating Sites: Weill Cornell Medicine,
PI: Mehraneh Dorna Jafari, MD
646-962 2342

Table of Contents

CONFIDENTIALITY STATEMENT VII

LIST OF ABBREVIATIONS VIII

1. PROTOCOL SUMMARY 1
1.1 Schema 3
1.2 Study Objectives and End Points 5
1.2.1 Primary Objectives 5
1.2.2 Secondary Objectives 5
1.2.3 Exploratory Objectives 5
1.2.4 Primary Endpoints 5
1.2.5 Secondary Endpoints 5

2. BACKGROUND 6
2.1 Disease 6
2.2 Investigational Agent/Device, or Surgical Treatment/Method 6
2.3 Rationale 8
2.4 Risk/Benefit Assessment 8
2.4.1 Known Potential Risks 8
2.4.2 Known Potential Benefits 9
2.4.3 Assessment of Potential Risks and Benefits 9
2.5 Correlative Studies Background 9

3. STUDY DESIGN 10
3.1 Overall Design 10
3.2 Scientific Rationale for Study Design 10
3.3 Justification for Dose 10
3.4 End of Study Definition 11

4. SUBJECT SELECTION 11
4.1 Study Population 11
4.2 Inclusion Criteria 11
4.3 Exclusion Criteria 11
4.4 Lifestyle Considerations 11
4.5 Screen Failures 11
4.6 Strategies for Recruitment and Retention 12

5. REGISTRATION PROCEDURES 12
5.1 Subject Registration (WCM only) 12
5.2 Subject Registration (Sub-sites) 12

6. STUDY PROCEDURES 12

6.1 Schedule of Assessments 12
6.1.1 Screening Visit (*-X days before start of treatment*) 13
6.1.2. Day of Surgery 13
Procedure Stage 13
Sample # 13
Time of collection 13
H2 13
CH4 13
CO2 13
CO2 flow/rate 13
Intraabdominal Pressure (mmHg) 13
Volume 13
Re-Insufflation 13
Y_N 13
Anesthetic gases 14
6.1.3 Follow-up Phase 14

7. STUDY INTERVENTION 14
7.1 Study Intervention/Device Description 14
7.2 Availability 14
7.3 Acquisition and Accountability 14
7.10 Duration of Follow Up 15
7.11 Measures to Minimize Bias: 15
This is a prospective pilot interventional, single-center, single-arm, open-label, phase 1 investigator-initiated study to determine device ability to detect bowel gas during laparoscopic right hemicolectomy with intracorporeal anastomosis using Perf-AlertTM gas detection system on 20 subjects into 2 Cohorts. To minimize the selection bias, we will enroll 20 consecutive subjects willing to participate in the study. The first 10 subjects will be part of Cohort 1, and the following 10 subjects will be part of Cohort 2. 15
7.12 Study Intervention/Follow-up Compliance 15

8. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 15
8.1 Discontinuation of Study Intervention 15
8.2 Participant Discontinuation/Withdrawal from the Study 15
8.3 Lost to Follow Up 16

9. CORRELATIVE/SPECIAL STUDIES 16
9.1 Laboratory Correlative Studies 16
9.1.1 Title – Laboratory Correlative Study #1 16
9.1.1.1 Collection of Specimen(s) 16
9.1.1.2 Handling of Specimen(s) 16
9.1.1.3 Shipping of Specimen(s) (if multicenter) 16

9.1.1.4 Site(s) Performing Correlative Study (if multicenter)....16
9.2 Special Studies....16
9.2.1 Title – Special Correlative Study #1....16
9.2.1.1 Assessment....16
9.2.1.2 Method of Assessment....16
9.2.1.3 Timing of Assessment....16

10. MEASUREMENT OF EFFECT....16
10.1 Response Criteria....16
10.2 Duration of Response....16
10.3 Progression-Free Survival....16
10.4 Other Response Parameters....16

11. DATA REPORTING / REGULATORY CONSIDERATIONS....16
11.1 Data Collection....16
11.1.1 Microsoft Access....17
11.2 Regulatory Considerations....17
11.2.1 Institutional Review Board/Ethics Committee Approval....17
11.2.2 Ethical Conduct of the Study....18
11.2.3 Informed Consent....18
11.2.4 Compliance with Trial Registration and Results Posting Requirements....18
11.2.5 Record Retention....18

12. STATISTICAL CONSIDERATIONS....18
12.1 Study Design/Endpoints....19
12.2 Sample Size/Accrual Rate....20
12.3 Stratification Factors....20
No stratification factors and no interim analysis will be done....20
12.4 Analysis of Endpoints....20
12.4.1 Analysis of Primary Endpoints....20
12.4.2 Analysis of Secondary Endpoints....21
12.5 Interim Analysis....21
12.6 Reporting and Exclusions....21
12.6.1 Evaluation of Toxicity....21
12.6.2 Evaluation of Response....21

13. ADVERSE EVENT REPORTING REQUIREMENTS....21
13.1 Adverse Event Definition....21
13.1.1 Investigational Agent or Device Risks (Expected Adverse Events)....22
13.1.2 Adverse Event Characteristics and Related Attributions....22
13.1.3 Recording of Adverse Events....22
13.1.4 Reporting of AE to WCM IRB....23
13.1.5 Reporting Events to Participants....23

Not Applicable. 23
13.1.6 Events of Special Interest- 23
Not Applicable. 23
13.1.7 Reporting of Pregnancy 23
13.2 Definition of SAE 23
13.2.1 Reporting of SAE to IRB 23
13.2.2 Reporting of SAE to FDA [For Protocols Where WCMC is the Sponsor-Investigator] 23
13.2.3 Reporting of SAE to Sentire Medical Systems, Inc. 24
13.3 AE/SAE Follow Up 24
13.4 Time Period and Frequency for Event Assessment and Follow Up 24

14. UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS 24
14.1 Definition of Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO) 24
14.1.2 Unanticipated Problem Reporting 25

15. DATA AND SAFETY MONITORING PLAN (DSMP) 25

Statement of Compliance

(1) [The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the <specify NIH Institute or Center (IC) > Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM, unless disclosure on ClinicalTrials.gov is federally required.

List of Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
CTSC	Clinical Translational Science Center
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
UIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
WCM	Weill Cornell Medicine

1. Protocol Summary

Full Title:	Evaluation of Ability to Detect Bowel Gas during Laparoscopic Right Colectomy with Intracorporeal Anastomosis
Short Title:	*Perf-Alert™ Pilot Study*
Clinical Phase:	*I*
Principal Investigator:	Mehraneh Dorna Jafari, MD
Study Description:	*Undetected bowel perforation is a rare but dangerous complication of laparoscopic surgery. If the injury is not detected and treated at the time of the surgical procedure, the patient can suffer severe complications, including septic shock and eventually death. Our goal is to test a novel device that can detect bowel gas leakage from perforation and alert the surgeon during the operation by evaluating the gases present in the insufflated abdomen during surgery. This study will determine the ability of the device to be attached to a standard trocar during the operation and periodically draw small samples or aliquots of gas from the abdomen to evaluate the gas and accurately detect gaseous content from the bowel. Before the device can be used to detect bowel perforations, we must first ensure that it can accurately detect bowel gas in an insufflated abdomen.*
Sample Size:	*N*= 20
Enrollment:	*This study will enroll 20 subjects and screen up to 50 subjects.*
Study Population:	*Participants of any gender over the age of 18 undergoing laparoscopic right colectomy with intracorporeal anastomosis procedures for regular care of their medical condition.*
Enrollment Period:	*12 months*
Study Design:	*Prospective pilot, interventional, single-center, single arm, open-label, investigator-initiated study of 20 subjects in 2 cohorts: Cohort 1- 10 subjects and Cohort 2- 10 subjects, to determine device ability to detect bowel gas during laparoscopic right hemicolectomy with intracorporeal anastomosis.*
Description of Sites/ Facilities Enrolling	*Single site study* Weill Cornell Medicine
Participants:	*20*
Study Duration:	*14 months from initiation to study completion (12 months accrual, 2 months data analyses and presentation).*
Participant Duration:	*4-6 weeks. From enrollment and consent during preoperative clinic visit (Visit 1) and during surgery (Visit 2). Data will be gathered preoperatively and intraoperatively during the laparoscopic right colectomy.*
Study Agent/Device Name	*Perf-AlertTM, Sentire Medical Systems, Inc., USA*
Intervention Description:	*The anesthesia and the laparoscopic surgical procedure will be performed as per standard of care. Perf-AlertTM was developed by Sentire Medical Systems, Inc., USA. The Perf-AlertTM prototype*

consists of a 15" x 13" x 7" unit containing gas sensors and valves, a small box containing a one-way, ultra-low pressure pump, user controls (buttons), and software algorithms, which control the operation of the device. It is used in conjunction with a single-use, disposable kit consisting of sterile tubing and filters used for sample collection and transport. The sensing unit will be connected via a sterile tube/filter set to any trocar port in use during the procedure. At specific time points during the procedure, a one-way valve will be opened, and the unit's pump turned on and withdrawing a small aliquot of gas from the abdominal cavity to the sensing unit. The system's architecture is configured such that sample collection, transport, analysis, and feedback occur in a single step such that sample collection and sensor feedback occur in real-time. A standard laptop running an analytical software program is connected to the unit to record and log sensor readings.

Primary Objective: *The primary objective of this study is to test the Perf-Alert™ device's ability to detect, in humans, bowel gas leakage [Hydrogen (H2) and Methane (CH4)] into an insufflated abdomen during laparoscopic right colectomy with intracorporeal anastomosis*

Secondary Objectives: *The secondary objective of this study is to determine response time of the Perf-Alert™ device.*

Exploratory Objectives: *N/A*

Primary Endpoints: Presence of Hydrogen (H2) and Methane (CH4) gas measured in ppm or mg/L (parts per million or milligrams per liter (mg/L) at 8 time points during the surgery:

1) Initiation of surgery/laparoscopy start Insufflation
2) Abdominal exploration
3) Completion of colon mobilization
4) Colon transection
5) At Colotomy
6) At Enterotomy
7) Anastomosis completion
8) End of surgery- after re-insufflation before closure

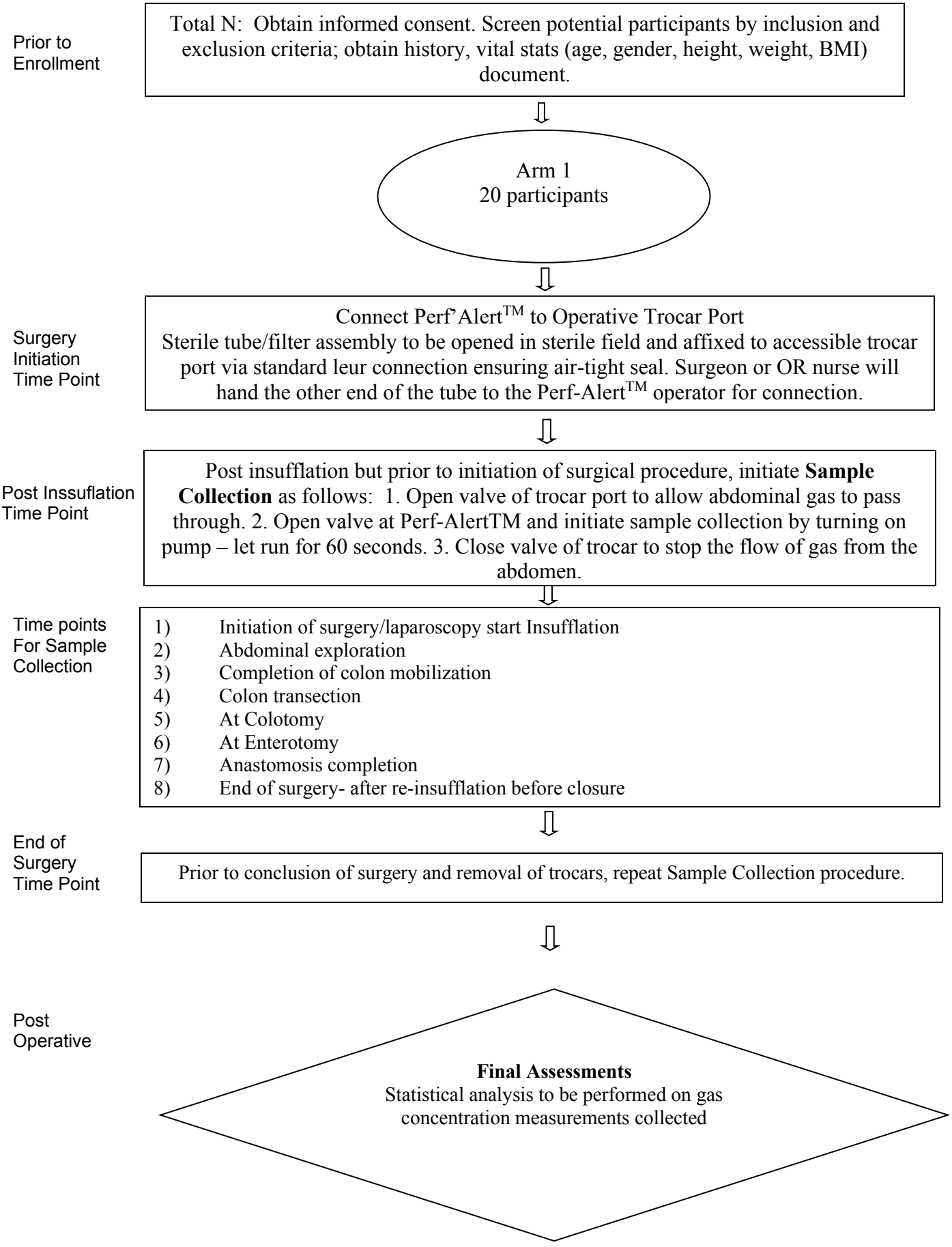
All data to be analyzed will be gathered during a single surgical procedure

Secondary Endpoints: The response time of the Perf-AlertTM device measured in seconds from obtaining the sample (from opening the valve to obtain sample) to first detecting a gas presence at the device electronic sensors.

Covariates:

Demographics
Preoperative Diagnosis
Existing Medical Conditions
Statin drugs in the last 3 months
Antibiotics in the last 3 months
Intra-abdominal pressure
Anesthetic gases
Total CO2 volume
Intraoperative complications

1.1 Schema


Prior to Enrollment
Total N: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, vital stats (age, gender, height, weight, BMI) document.
Arm 1
20 participants
Surgery Initiation Time Point
Connect Perf'Alert™ to Operative Trocar Port
Sterile tube/filter assembly to be opened in sterile field and affixed to accessible trocar port via standard leur connection ensuring air-tight seal. Surgeon or OR nurse will hand the other end of the tube to the Perf-Alert™ operator for connection.
Post Inssuflation Time Point
Post insufflation but prior to initiation of surgical procedure, initiate **Sample Collection** as follows: 1. Open valve of trocar port to allow abdominal gas to pass through. 2. Open valve at Perf-AlertTM and initiate sample collection by turning on pump – let run for 60 seconds. 3. Close valve of trocar to stop the flow of gas from the abdomen.
Time points For Sample Collection
1) Initiation of surgery/laparoscopy start Insufflation
2) Abdominal exploration
3) Completion of colon mobilization
4) Colon transection
5) At Colotomy
6) At Enterotomy
7) Anastomosis completion
8) End of surgery- after re-insufflation before closure
End of Surgery Time Point
Prior to conclusion of surgery and removal of trocars, repeat Sample Collection procedure.
Post Operative
Final Assessments
Statistical analysis to be performed on gas concentration measurements collected

1.2 Study Objectives and End Points

1.2.1 Primary Objectives

To test the Perf-Alert™ device's ability to detect, in humans, bowel gas leakage [Hydrogen (H2) and Methane (CH4)] into an insufflated abdomen during laparoscopic right large intestinal surgery with intracorporeal anastomosis.

1.2.2 Secondary Objectives

The secondary objective of this study is to determine response time of the Perf-Alert™ device.

1.2.3 Exploratory Objectives

N/A

1.2.4 Primary Endpoints

The primary end points are the presence of Hydrogen (H2) and Methane (CH4) gas measured in ppm or mg/L (parts per million or milligrams per liter (mg/L) at 8 time points during the surgery.

1) Initiation of surgery/laparoscopy start Insufflation
2) Abdominal exploration
3) Completion of colon mobilization
4) Colon transection
5) At Colotomy
6) At Enterotomy
7) Anastomosis completion
8) End of surgery- after re-insufflation before closure

Initiation of surgery and end of surgery. All data to be analyzed will be gathered during a single surgical procedure.

1.2.5 Secondary Endpoints

The response time of the Perf-AlertTM device measured in seconds from obtaining the sample (from opening the valve to obtain sample) to first detecting a gas presence at the device electronic sensors.

1.2.6 Covariates:

Demographics
Preoperative Diagnosis
Existing Medical Conditions
Statin drugs in the last 3 months
Antibiotics in the last 3 months
Intra-abdominal pressure

Anesthetic gases
Total CO2 volume
Intraoperative complications

2. Background

2.1 Disease

Undetected intraoperative bowel injuries are rare but devastating complications of laparoscopic surgery. Intraoperative small and large intestinal injuries have been reported in the range of 0.1-9.2%, and 1.3-4.8% are diagnosed after surgery [1-3]. Multiple risk factors are described in the literature to play a role in the iatrogenic bowel injuries such as lysis of adhesions, history of previous abdominal surgery, electrocautery, utilization of grasping forceps or scissor, obesity, bowel obstruction, and restricted visual field [1-7]. Further, laparoscopic procedures such as large bowel resections with anastomosis can often develop leaks leading to similar complications including severe morbidity and mortality. The leak test is one method of testing for anastomotic leak after completion of bowel anastomosis, although some studies show it has not significantly decreased the anastomotic leak occurrence [8]. Another intervention to prevent the occurrence of an anastomotic leak or to decrease the severity of the leak after the occurrence is diverting stoma creation, with conflicting reports on its role in leak prevention [9]. If the injury is not detected and treated at the time of the surgical procedure, the patient can suffer severe complications including septic shock and eventually death [1, 7-12].

A novel alternative method for early detection of intraoperative bowel injuries may help to avoid or decrease some of the most dreadful postoperative complications such as peritonitis, septic shock, and eventually death. Bowel gases Hydrogen (H2) and Methane (CH4) are only two of the gases produced in the large intestine as a by-product result of bacterial fermentation [12-13]. When the bowel is injured or intentionally opened during surgery, these gases escape into the abdominal cavity and could be useful for early detection of bowel injury. Sentire Medical Systems, USA has developed a novel device that may be able to detect these gases during surgery. Unpublished data from preclinical studies show that the device sensors were able to detect small quantities of hydrogen and methane gases within 30 seconds of analysis [12]. The first human trial with 8 patients undergoing Roux-en-y gastric bypass reported that hydrogen gas was detected by the Sentire device in real-time during surgery, and suggested that the device could be used for the detection of iatrogenic intraoperative bowel injuries [12].
This study aims to test the Perf-AlertTM device's ability to detect, in humans, bowel gas leakage [Hydrogen (H2) and Methane (CH4)] into an insufflated abdomen during laparoscopic right colon surgery with intracorporeal anastomosis.

2.2 Investigational Agent/Device, or Surgical Treatment/Method

Our goal is to test a novel device that can detect bowel gas leakage from perforation and alert the surgeon during the operation by evaluating the gases present in the insufflated abdomen during surgery. During laparoscopic surgery, CO2 is inserted into the abdominal cavity in order to perform the operation. This is a dynamic process as insufflation is constant during the entire procedure to maintain constant pressure and compensate for any small leaks due to the insertion and retrieval of instruments.

This study will determine the ability of a novel device to be attached to a standard trocar during the operation and periodically draw a small amount of gas from the abdomen to evaluate the gas and

accurately detect gaseous content from the bowel. Before the device can be used to detect bowel perforations, first we must ensure that it can accurately detect bowel gas in an insufflated abdomen.

The Investigational device, Perf-AlertTM, consists of a 15” x 13” x 7” unit containing gas sensors and valves, a small box containing a one way, ultra-low pressure pump, user controls (buttons), and software algorithms, which control the operation of the device (Image1). It is used in conjunction with a single-use, disposable kit consisting of sterile tubing and filters used for sample collection and transport (Image 2). The sensing unit will be connected via a sterile tube/filter set to any trocar port in use during the procedure. At specific time points during the procedure, a one-way valve will be opened and the unit’s pump turned on pulling small aliquots of gas from the abdominal cavity to the sensing unit. The system’s architecture is configured such that sample collection, transport, analysis, and feedback occur in a single step such that sample collection and sensor feedback occur in real-time. A standard laptop running an analytical software program is connected to the unit to record and log sensor readings. No changes to the device are anticipated during the course of the study.

Image1. Investigational device, Perf-Alert™

Image 2. A single use, disposable kit consisting of sterile tubing and filters

2.3 Rationale

Undetected bowel perforation is a rare but dangerous complication of laparoscopic surgery. If the injury is not detected and treated at the time of the surgical procedure, the patient can suffer severe morbidity, including septic shock and eventually death. Inadvertent and undetected bowel perforations have occurred during laparoscopic surgeries of all types: cholecystectomy, hernia repair, hysterectomy, oophorectomy, etc. Further, laparoscopic procedures involving the bowel, such as bariatric (foregut) and colorectal (bowel resections and anastomosis), can often develop leaks leading to similar complications, including severe morbidity and mortality [1, 7-9]. This research is important to the colorectal surgery field as it may provide an alternative for early detection of bowel injury or anastomosis leak during the intraoperative time, and thus avoid or decrease some of the most dreadful postoperative complications such as peritonitis, septic shock, and eventually death.

2.4 Risk/Benefit Assessment

2.4.1 Known Potential Risks

No changes in the care or treatment of the patients will be made as a result of this study, it is only intended to be observational, and therefore, minimal risk is anticipated. The technology being studied will not come into direct contact with the patient. A sterile tubing will be connected to the trocar in the patient during the operation. As sterile tubing is routinely connected to trocars, there is little to no physical risk to the patient. The same type of tubing and setup will be used for measurements as the one used for the insufflation of CO_2.

Another potential physical risk is the time under anesthesia. The additional amount of time that the patient will be under anesthesia due to the collection of the gas samples will be under 5 minutes, mitigating any increased risk to the patients due to a long duration under anesthesia.

Another potential physical risk is the need to ex-sufflate and re-insufflate the abdomen prior to the final gas sample collection. Ex-sufflation and re-insufflation occur routinely during laparoscopic surgery due to instrument exchange, and since there will be no instruments in the patient during this ex-sufflation/re-insufflation, the risk to the patient will be no higher than the risk during the regular surgical procedure. The surgeon and study personnel will be responsible for triggering the device to sample the intra-abdominal gas at the predefined time points, they will not have direct contact with any bodily fluids or gases. Therefore, we do not anticipate any significant risks or exposure risks to the patients or study personnel.

Finally, a previous clinical study involving the roux-en-y bariatric procedure was conducted with no adverse patient events [11]' Information on this study is available at Clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT02679118?term=Sentire&cond=Bowel+Perforation&cntry=US&rank=1)

Another potential risk related to this research is the loss of privacy. However, all the necessary measures will be taken to protect the subject's privacy. The electronic data will be kept in password-protected computers and the paper data will be stored in a locked cabinet in the locked research office located at K802B.

2.4.2 Known Potential Benefits

There will not be any direct benefits to the participating subjects. This device is not intended to treat or to alter treatment, therefore we do not expect there to be any benefit to the participating subjects in this study.

We hope the information learned from this study will lead to the development of a solution that could minimize intraoperative bowel injury and would be of significant benefit to future patients and providers.

2.4.3 Assessment of Potential Risks and Benefits

Given the potential benefits offered by minimizing one of the most consequential and costly complications of laparoscopy, the potential risks of the study are minimal. Specifically, the device to be investigated will not come into contact with the patient at any time and is simply connected via a standard tube set to a trocar in use during the procedure. The tubing utilized is the same as that used to connect the insufflator to the trocar and standard in all laparoscopic procedures. Secondly, the surgeon will not alter the procedure in any way, with the exception of 60-90 second pauses at each time point during sample collection. The total additional anesthesia time required for each subject will be less than 5 minutes. We believe the benefits of this study overweight the risk.

2.5 Correlative Studies Background

Not Applicable

3. Study Design

3.1 Overall Design

Research question: Can detectable levels of bowel gas methane (CH4) and/or hydrogen (H2) be detected in the abdominal cavity when the bowel is open during laparoscopic right colectomy with intracorporeal anastomosis using Perf-Alert™ detection system?

Research Hypothesis: H1: Bowel gas, methane (CH4) and/or hydrogen (H2) can be detected in the abdominal cavity when the bowel is open during laparoscopic right colectomy with intracorporeal anastomosis using the Perf-Alert™ detection system.

Design
Prospective pilot, single-center, single arm, open label, phase 1 investigator-initiated study to determine device ability to detect bowel gas during laparoscopic right colectomy with intracorporeal anastomosis using Perf-Alert™ gas detection system on 20 subjects into 2 Cohorts.

Cohort 1: 10 subjects with measurement of bowel gas at 8 predetermined time points during right laparoscopic colectomy as follow:

1) Initiation of surgery/laparoscopy start Insufflation
2) Abdominal exploration
3) Completion of colon mobilization
4) Colon transection
5) At Colotomy
6) At Enterotomy
7) Anastomosis completion
8) End of surgery- after re-insufflation before closure

Cohort 2: 10 subjects with continuous monitoring of bowel gases through the surgery. The level of H2 and CH4 gases will be noted at the 8 predetermined time points during the continuous monitoring as well.

3.2 Scientific Rationale for Study Design

Preliminary investigation of a novel device to detect intraoperative bowel perforation/leak during right laparoscopic colectomy. The study will include a prospective quantitative assessment of intra-abdominal gaseous content during intracorporeal anastomosis procedures to determine the detectability of bowel gas or lack thereof when the bowel is intact and open. All study participants will be subject to the same protocol, and there will be no control group given the nature of the study and desired data. Each subject will be its own control using the baseline measurement as reference. For a phase one preliminary investigation, this design is appropriate because we cannot collect the study samples in a retrospective fashion, and the data from the prospective cohorts will provide the necessary information to test the study hypothesis and answer the research question.

3.3 Justification for Dose

Not Applicable

3.4 End of Study Definition

A clinical trial is considered completed when participants are no longer being examined or the last participant's last study visit has occurred. For this study it will be after subject 20 has completed the surgery.
A participant is considered to have completed the study if he or she has right laparoscopic colectomy with intracorporeal anastomosis completed.

4. Subject Selection

4.1 Study Population

Subjects who are undergoing right laparoscopic colectomy with intracorporeal anastomosis for regular care of their medical condition, and who meet the inclusion and exclusion criteria will be eligible for participation in this study.

4.2 Inclusion Criteria

1. Male or female ≥ 18 years of age.
2. Documentation of a required elective right laparoscopic hemicolectomy with intracorporeal anastomosis
3. Subject signed inform consent

4.3 Exclusion Criteria

1. Less than 18 years old
2. Pregnant or breastfeeding
3. Patients undergoing emergency laparotomy for perforated right colon or trauma
4. Patients with Intraabdominal abscess, peritonitis or enteric fistula
5. Patients who are on peritoneal dialysis
6. Subjects do not speak English

4.4 Lifestyle Considerations

Not applicable

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

In this study, subjects who have signed the consent but do not meet the inclusion and exclusion criteria listed in sections 4.2 and 4.3 will be considered screen failures.

4.6 Strategies for Recruitment and Retention

The potential subjects for this study will be identified from the practice of the Colon and Rectal Surgery, through screening of the daily schedule on EPIC. Subjects scheduled for right laparoscopic colectomy with intracorporeal anastomosis for regular treatment of their medical condition will be invited to participate in the study. The subjects willing to participate in the study will be presented with the research informed consent and introduced to the study. Subject understanding of the study will be assessed, and a full understanding of the study has to be demonstrated by the subject before they sign consent. The subjects will be recruited during the preoperative clinic visit or while in-patient
We are targeting to recruit 20 subjects, male and female, of all ethnic groups. No vulnerable populations will be included in the study. The current colorectal practice includes 8 surgeons, and with no competing study, we believe that we will be able to recruit these subjects for 12 months. The participants will not be compensated for their participation in the study. Also, there are no extra visits that have to be made due to the research study. All the procedures are standard of care, except the gas samples.

5. Registration Procedures

5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

5.2 Subject Registration (Sub-sites)

Not applicable

6. Study Procedures

6.1 Schedule of Assessments

Table 1. Schedule of trial events

	Before Surgery	Day 0 Surgery	Post op In Hospital	30 ±2 days Follow Up
Informed consent	X			
Inclusion/ Exclusion	X			
Demographics	X			
Medical history	X			
Medication	X			
Intraoperative data		X		
Hydrogen H2 Samples		X		
Methane Samples CH4		X		
Anesthetic gases				

Post op data			X	X

6.1.1 Screening Visit (*30 days before start of treatment*)

- *Informed consent*
- *Medical history*
- *Physical exam*
- *Medications*
- *Collect vital statistics – age, gender*

6.1.2. Day of Surgery

- *Intraoperative data*
- *Hydrogen H2 Samples*
- *Methane CH4 Samples*
- *CO2 flow/rate*
- *Intraabdominal Pressure (mmHg)*
- *Anesthetic gases*
- *Total Volume CO2*

Sample Collection Table

Procedure Stage	Laparoscopy Start Insufflation	Abdominal Exploration	Completion of Colon mobilization	Colon transection	At Colotomy	At Enterotomy	After anastomosis completion	Re-Insufflation Before Closure
Sample #	**S1_Baseline**	**S2**	**S3***	**S4***	**S5**	**S6**	**S7**	**S8**
Time of collection								
H2								
CH4								
CO2								
CO2 flow/rate								
Intraabdominal Pressure (mmHg)								
Volume								
Re-Insufflation Y_N								

Anesthetic gases								

*- Collect sample before smoke evacuation

6.1.3 Follow-up Phase

Subjects will be followed postoperatively up to discharge from hospital and once again at 30 ±2 days after surgery. Relevant post-surgical complications will be collected.

7. Study Intervention

The anesthesia and the laparoscopic right colon surgery will be performed as per standard regular care.

7.1 Study Intervention/Device Description

The Perf-AlertTM device consists of a 15” x 13” x 7” unit containing gas sensors and valves, an ultra-low pressure pump, user controls (buttons), and software algorithms, which control the operation of the device. It is used in conjunction with a single-use, disposable kit consisting of sterile tubing and filters used for sample collection and transport. The sensing unit will be connected via a sterile tube/filter set to any trocar port in use during the procedure. At specific time points during the procedure, a one-way valve will be opened, and the unit’s pump turned on is withdrawing small aliquots of gas from the abdominal cavity to the sensing unit. The system’s architecture is configured such that sample collection, transport, analysis, and feedback occur in a single step such that sample collection and sensor feedback occur in real-time. A standard laptop running an analytical software program is connected to the unit to record and log sensor readings. The device will sit outside the sterile operative field and operated by a study coordinator with a representative of the device manufacturer present in the operating for troubleshooting.

7.2 Availability

Perf-Alert^{TM} is an investigational device supplied to investigators by Sentire Medical Systems, Inc. for the duration of the study

7.3 Acquisition and Accountability

Perf-ALert™ is an investigational device supplied to investigators by Sentire Medical Systems, Inc. for the duration of the study. The device will be stored at the research office located at K802C. The device will be examined by the Biomedical Engineering in the Greenberg Operating Rooms and will be approved for use in the operating room.

7.10 Duration of Follow Up

Not applicable

7.11 Measures to Minimize Bias:

This is a prospective pilot interventional, single-center, single-arm, open-label, phase 1 investigator-initiated study to determine device ability to detect bowel gas during laparoscopic right hemicolectomy with intracorporeal anastomosis using Perf-AlertTM gas detection system on 20 subjects into 2 Cohorts. To minimize the selection bias, we will enroll 20 consecutive subjects willing to participate in the study. The first 10 subjects will be part of Cohort 1, and the following 10 subjects will be part of Cohort 2.

7.12 Study Intervention/Follow-up Compliance

Subjects will be followed up to 30 ±2 days after surgery

8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

8.1 Discontinuation of Study Intervention

Any irregularity or complication during the surgery being performed will be grounds for discontinuation of the study intervention and withdrawal of the subject from the study. If the laparoscopic surgery has to be converted to an open surgical approach due to medical reasons or technical reasons, the study intervention will be discontinued and the subject withdrawn from the study.

No data will be collected at the time of study intervention discontinuation, and any data previously collected will be excluded from the study analysis and appropriately destroyed.

8.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

The reason for participant discontinuation or withdrawal from the study will be recorded on the on the intraoperative Case Report Form (CRF) and reflected in the WCMC subject registration site. Subjects who sign the informed consent form but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study will be replaced.

8.3 Lost to Follow Up

The participant's role in the study is completed at 30 days during which time all data is collected. The subject are coming regularly up to 30 days postop follow up, so we do not anticipate lost to follow up.

9. Correlative/Special Studies

Not applicable

9.1 Laboratory Correlative Studies

9.1.1 Title – Laboratory Correlative Study #1

9.1.1.1 Collection of Specimen(s)

9.1.1.2 Handling of Specimen(s)

9.1.1.3 Shipping of Specimen(s) (if multicenter)

9.1.1.4 Site(s) Performing Correlative Study (if multicenter)

9.2 Special Studies

9.2.1 Title – Special Correlative Study #1

9.2.1.1 Assessment

9.2.1.2 Method of Assessment

9.2.1.3 Timing of Assessment

10. Measurement of Effect

10.1 Response Criteria

Measurement of gastrointestinal gases (CH4 and/or H2) when the bowel is in an open condition will constitute a positive response for this study.

10.2 Duration of Response

Not applicable

10.3 Progression-Free Survival

Not Applicable

10.4 Other Response Parameters

Not applicable

11. Data Reporting / Regulatory Considerations

11.1 Data Collection

The data collection plan for this study is to utilize RedCap and the device data from the gas sample analyses.

11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.

All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites, as applicable. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval

before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB requirements, applicable laws and regulations.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.
This study will be registered on clinicaltrials.gov.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subjects medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

12. Statistical Considerations

12.1 Study Design/Endpoints

Research question: Can detectable levels of bowel gas methane (CH4) and/or hydrogen (H2) be detected in the abdominal cavity when the bowel is open during laparoscopic right colectomy with intracorporeal anastomosis using Perf-Alert™ detection system?

Research Hypothesis: H1: Bowel gas, methane (CH4) and/or hydrogen (H2) can be detected in the abdominal cavity when the bowel is open during laparoscopic right colectomy with intracorporeal anastomosis using the Perf-Alert™ detection system.

Design
Prospective pilot, single-center, single arm, open label, phase 1 investigator-initiated study to determine device ability to detect bowel gas during laparoscopic right colectomy with intracorporeal anastomosis using Perf-Alert™ gas detection system on 20 subjects into 2 Cohorts.

Cohort 1: 10 subjects with measurement of bowel gas at 8 predetermined time points during right laparoscopic colectomy as follow:

Initiation of surgery/laparoscopy start Insufflation
2) Abdominal exploration
3) Completion of colon mobilization
4) Colon transection
5) At Colotomy
6) At Enterotomy
7) Anastomosis completion
8) End of surgery- after re-insufflation before closure

Cohort 2: 10 subjects with continuous monitoring of bowel gases through the surgery. The level of H2 and CH4 gases will be noted at the 8 predetermined time points during the continuous monitoring as well.

Primary end point

Level of Hydrogen (H2) and Methane (CH4) gas measured in ppm or mg/L (parts per million or milligrams per liter (mg/L) at 8 time points during the surgery:

Initiation of surgery/laparoscopy start Insufflation
2) Abdominal exploration
3) Completion of colon mobilization
4) Colon transection
5) At Colotomy
6) At Enterotomy
7) Anastomosis completion
8) End of surgery- after re-insufflation before closure

Secondary endpoint

The response time of the Perf-AlertTM device measured in seconds from obtaining the sample (from opening the valve) to first detecting a gas presence at the device electronic sensors.

Covariates:

- Demographics
- Preoperative Diagnosis
- Existing Medical Conditions
- Statin drugs in the last 3 months
- Antibiotics in the last 3 months
- Intra-abdominal pressure
- Anesthetic gases
- Total CO2 volume
- Intraoperative complications

12.2 Sample Size/Accrual Rate

As this is a pilot study, a sample of 20 consecutive subject corresponding to the inclusion and exclusion criteria will accrued for the two study cohorts. Cohort 1- 10 subjects and Cohort 2- 10 subjects.

12.3 Stratification Factors

No stratification factors and no interim analysis will be done.

12.4 Analysis of Endpoints

12.4.1 Analysis of Primary Endpoints

The gas sample gas composition will be analyzed automatically by the Perf-AlertTM gas detection system at the 8 different predetermined time points listed in 12.1. The measurements will be recorded in the data collection forms. The maximum value for the particular sample gases – H2 and CH4, will be recorded and included in the descriptive analysis.

Specifically, the presence of Hydrogen (H2) and Methane (CH4) gas measured in ppm or mg/L (parts per million or milligrams per liter (mg/L) at the 8 time points during the surgery will be descriptively assessed. Descriptive statistics (e.g., mean, standard deviation, median, interquartile range, frequency and percent) will be calculated for these parameters. Ninety-five percent confidence intervals will be calculated for all parameters of interest to assess the precision of the obtained estimates. No formal hypothesis testing will be performed in the pilot study. However, pairwise time point comparisons will be evaluated by the paired t-test or Wilcoxon signed-rank test, as appropriate. Due to the small sample size in this pilot study, all analyses will be considered exploratory and hypothesis-generating with no adjustment for multiple comparisons. All *p*-values will be two-sided with statistical significance evaluated at the 0.05 alpha level. All analyses will be

conducted using SPSS for Windows v.25 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp).

12.4.2 Analysis of Secondary Endpoints

Descriptive analysis with measurements of central tendency and dispersion will also be used for the secondary endpoints presentation.

12.5 Interim Analysis

Not Applicable

12.6 Reporting and Exclusions

12.6.1 Evaluation of Toxicity

Not applicable

12.6.2 Evaluation of Response

Not applicable

13. Adverse Event Reporting Requirements

This study will not report specific adverse events, as subjects are undergoing surgery for regular care. Furthermore, the device that will be used to collect and analyze the bowel gases from the abdominal cavity during surgery is not in direct contact with subjects and does add additional physical risk to the subjects. During laparoscopy, the abdominal cavity is being insufflated with carbon dioxide (CO_2) gas, and a standard pressure between 12mm -15 mm/Hg is maintained throughout the surgery in the abdominal cavity for visualization through a CO_2 insufflation tubing connected with one of the surgical trocars. If the pressure changes, for example, during instrument exchange through the laparoscopic port, the CO_2 insufflator automatically starts the CO_2 flow, so the pressure could be maintained between 12mm -15 mm/Hg. When a gas sample for the study is collected from the abdominal cavity, the insufflator will simultaneously replace any volume of gas removed with new CO_2 gas. Therefore, there is no additional risk to the patient due to the gas sample collection for research during the surgery. All the intraoperative complications, should there be any, would be part of the regular surgical care risk.
However, all intraoperative complications will be collected as part of the study data collection. Also, to ensure safety, the intra-abdominal pressure level will be collected as a data point at the time of sample collection as part of the safety monitoring measure.

Any hydrogen (H_2) and methane (CH_4) detected by the device at time points when clinically, these gases are not expected to be found in the abdominal cavity, the operating surgeon will be notified.

13.1 Adverse Event Definition

This study does not have specific adverse events. All the interventions are part of regular surgical care. The device is not in direct contact with the subject during the surgery. Obtaining the gas sample will remove about 500 ml of gas for 90 seconds (1.5 minutes), which is

automatically replaced by the CO2 inflow simultaneous with gas sample collection. Therefore, it is not anticipated the abdominal pressure to decrease below 12 mm/Hg.

13.1.1 Investigational Agent or Device Risks (Expected Adverse Events)

We believe this is a nonsignificant risk device as the device and the expected risk is no more than the minimal risk.
The device:

- Does not come into direct contact with the subject during the surgery
- Does not introduce any energy to the subject

Further, the device will be labeled appropriately and examined by the biomedical engineering at operating rooms at WCMC-NYPH.

13.1.2 Adverse Event Characteristics and Related Attributions

Not Applicable

Specify the adverse event reporting system you will utilize for tracking adverse events during the conduct of this study (i.e., NCI Common Terminology Criteria for Adverse Events (CTCAE), Vaccine Adverse Event Reporting System (VAER), Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Manufacturer and User Facility Device Experience Database (MAUDE) and the Special Nutritionals Adverse Event Monitoring System).

For example, the following text is text that may be used when utilizing the CTCAE and should be changed to reflect the correct AE reporting system.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

13.1.3 Recording of Adverse Events

While this study will not report adverse events related to the study, the study will collect all the intraoperative complications and record them on the data collection forms in the subject's research chart. All complications, should there be any, will be recorded in the subject's medical record as they are part of the regular surgical care.
We do not have expected adverse events related to the Perf-AlertTM device use. However, we are reporting unanticipated problems/ unexpected adverse events, which include if the Perf-AlertTM device stopping work during surgery or malfunction, and these events will be reported to the IRB,

and the device's sponsor Sentire Medical Systems, Inc., USA. This is described in section 14.1.2 of the protocol and is now added to sections 13.1.3 and 13.2.3 of the protocol. In general, we are collecting intraoperative and postoperative complications.

13.1.4 Reporting of AE to WCM IRB

This study will not be reporting AE.

13.1.5 Reporting Events to Participants

Not Applicable.

13.1.6 Events of Special Interest-

Not Applicable.

If applicable, include content in this section otherwise type "Not Applicable."

13.1.7 Reporting of Pregnancy

Not Applicable.

13.2 Definition of SAE

SAEs include death, life threatening adverse experiences, prolongation of hospitalization, disability or incapacitation, and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

13.2.1 Reporting of SAE to IRB

Not Applicable.

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.2.2 Reporting of SAE to FDA [For Protocols Where WCMC is the Sponsor-Investigator]

Not Applicable.

IND application sponsor must report any suspected adverse reaction or adverse reaction to study treatment that is both serious and unexpected. Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to FDA as soon as possible but no later than 7 calendar days following the sponsor's initial receipt of the information.

i. death,
ii. a life-threatening adverse event,
iii. in-patient hospitalization or prolongation of existing hospitalization,
iv. a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
v. a congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or research subject and may require medical or surgical intervention to prevent one of the outcomes listed as serious

CDER INDs:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of *xxxx* Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

CDER-only Biologic INDs:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biologic Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

CBER INDs:

Office of *xxxx*
Center for Biologics Evaluation and Research
Food and Drug Administration
Suite 200N 1401 Rockville Pike
Rockville, MD 20852-1448

13.2.3 Reporting of SAE to Sentire Medical Systems, Inc.

We are reporting Unanticipated Problems/ Unexpected adverse events which include the Perf-AlertTM device stop working during surgery, or malfunction, and these events will be reported to the IRB and the device sponsor Sentire Medical Systems, Inc.,USA. This is described in section 14.1.2 of the protocol, and now added to In general we are collecting intraoperative and postoperative complications.

13.3 AE/SAE Follow Up

Not Applicable.

13.4 Time Period and Frequency for Event Assessment and Follow Up

Not Applicable

14. Unanticipated Problems Involving Risks to Subjects or Others

14.1 Definition of Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)

In this study, unanticipated adverse device effect will be defined as any unanticipated adverse device effect, any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).]

14.1.2 Unanticipated Problem Reporting

The investigator will submit to the sponsor Sentire Medical Systems, Inc. and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)), A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b) (1)).

15. Data and Safety Monitoring Plan (DSMP)

To ensure the safety of clinical research subjects and protect the validity and integrity of research data, subjects will be well acquainted with the research study prior to signing research informed consent. Further, the subjects will be selected strictly according to the study inclusion and exclusion criteria. The electronic data collected as part of this study will be stored in a password-protected computer, and the paper data will be locked in the locked cabinet in the clinical research office located at K802C. We do not anticipate any adverse events related to this study. However, all intraoperative surgical complications will be collected as part of this study data. We will report unanticipated adverse events to the WCMC IRB and to Sentire Medical Systems.

16. References

1) Leevan, E., & Carmichael, J. C. (2019, September). Iatrogenic bowel injury (early vs delayed). In Seminars in Colon and Rectal Surgery (Vol. 30, No. 3, p. 100688). WB Saunders.
2) Behman, R., Nathens, A. B., Byrne, J. P., Mason, S., Hong, N. L., & Karanicolas, P. J. (2017). Laparoscopic surgery for adhesive small bowel obstruction is associated with a higher risk of bowel injury: a population-based analysis of 8584 patients. Annals of Surgery, 266(3), 489-498.
3) Suter, M., Zermatten, P., Halkic, N., Martinet, O., & Bettschart, V. (2000). Laparoscopic management of mechanical small bowel obstruction. Surgical endoscopy, 14(5), 478-483.
4) Stommel, M. W., Strik, C., ten Broek, R. P., de Wilt, J. H., & van Goor, H. (2016). Impact of adhesiolysis on outcome of colorectal surgery. *Digestive Surgery*, *33*(2), 83-93.
5) Yamamoto, M., Okuda, J., Tanaka, K., Kondo, K., Asai, K., Kayano, H., ... & Uchiyama, K. (2013). Effect of previous abdominal surgery on outcomes following laparoscopic colorectal surgery. Diseases of the colon & rectum, 56(3), 336-342.
6) Kin, C., Snyder, K., Kiran, R. P., Remzi, F. H., & Vogel, J. D. (2013). Accidental puncture or laceration in colorectal surgery: a quality indicator or a complexity measure?. Diseases of the colon & rectum, 56(2), 219-225.
7) Llarena, N. C., Shah, A. B., & Milad, M. P. (2015). Bowel injury in gynecologic laparoscopy: a systematic review. Obstetrics & Gynecology, 125(6), 1407-1417.
8) Wu, Z., van de Haar, R. C., Sparreboom, C. L., Boersema, G. S., Li, Z., Ji, J., ... & Lange, J. F. (2016). Is the intraoperative air leak test effective in the prevention of colorectal anastomotic leakage? A systematic review and meta-analysis. International journal of colorectal disease, 31(8), 1409-1417.
9) Floodeen, H., Hallböök, O., Hagberg, L. A., & Matthiessen, P. (2017). Costs and resource use following defunctioning stoma in low anterior resection for cancer–A long-term analysis of a randomized multicenter trial. European Journal of Surgical Oncology (EJSO), 43(2), 330-336.
10) Martin, K. E., Moore, C. M., Tucker, R., Fuchshuber, P., & Robinson, T. (2016). Quantifying inadvertent thermal bowel injury from the monopolar instrument. Surgical endoscopy, 30(11), 4776-4784.
11) Künzli, B. M., Spohnholz, J., Braumann, C., Shrikhande, S. V., & Uhl, W. (2018). Clinical Impact of Iatrogenic Small Bowel Perforation Secondary to Laparoscopic Cholecystectomy: A Single-center Experience. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques, 28(5), 309-313.
12) Wynne, E.K., Azagury, D.E. Novel device to detect enterotomies in real time during laparoscopy: first in human trial during Roux-en-y gastric bypass. Surg Endosc 33, 1687–1692 (2019). https://doi.org/10.1007/s00464-018-06637-2
13) Sahakian, A. B., Jee, S. R., & Pimentel, M. (2010). Methane and the gastrointestinal tract. Digestive diseases and sciences, 55(8), 2135-2143.