Cover Page for Study Protocol

Sponsor-Investigator:	Jennifer Hrabe
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Official Title:	Optimizing the Previs Device for Prediction of Postoperative Ileus
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Device Name:	Previs Device
Title of Study:	Optimizing the Previs device for Prediction of Postoperative Ileus (Previs Optimization)
Study Center:	University of Iowa
Estimated number of subjects:	475 subjects (50% male, 50% female) will be recruited and enrolled in this study.
Study Period:	February 2018 until completion
Estimated date of first enrollment:	February 2018 will be the earliest day of enrollment, pending approval from UI IRB.
Estimated date of last enrollment:	We estimate that all subjects will be enrolled by January 2020.
Sponsor:	Entac Medical, Inc.
Version:	4.0
Date:	September 28, 2020

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I. Statement of Compliance:

This study will be conducted in compliance with the protocol, Good Clinical Practice and the applicable Food and Drug Administration and other Department of Health and Human Services regulatory requirements.

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection and Good Clinical Practice training.

II. IRB Oversight:

Human Subjects Office / IRB
J. Andrew Bertolatus, MD
Hardin Library, Office 105
600 Newton Rd
Iowa City, IA 52242
FWA#: FWA00003007
Voice: 319-335-6564
Fax: 319-335-7310
Email: irb@uiowa.edu

III. Location of Study Procedures:

University of Iowa Hospitals and Clinics (UIHC)
200 Hawkins Drive
Iowa City, Iowa 52242

IV. Trial Design:

This is a prospective, non-randomized, open label, single center study designed to assess and optimize performance of the Previs device.

V. Study Aims:

The aims of this study are:

1) To incorporate digital signal processing algorithms and design changes from prior trials into a re-designed prototype, self-contained, noninvasive device that retains or improves the predictive accuracy.

2) To continue making iterative refinements on prototype device design to one that reliably performs in a health care environment.

VI. Main Screening Criteria:

We will recruit men and non-pregnant women of any ethnic background between the age ≥ 18 and ≤ 100 years that are scheduled to undergo an elective intestinal resection surgery by the colorectal surgery service at UIHC.

VII. Screening/Recruitment procedures:

Adult patients presenting to the Digestive Health Center at UIHC for elective intestinal resection surgery or to Urology Clinic at UIHC for cystectomy, that qualify, will be offered participation in the trial. Study team will review potential subject's chart for possible inclusion/exclusion criteria. This pre-screening is done so that potential subjects and their families are not approached until the study team reviews and verifies that it would appear that the subject may qualify.

The study team will approach the potential subject and tell them that they may qualify for a study and ask if they are interested in hearing about the study. If the potential subject is interested, the study will be explained to them in detail. They will be encouraged to ask questions and talk it over with the treating physician and family members.

If the potential subject would like to participate, one of the members of the study team will go over the consent form with them, answering any questions they may have as the study team goes through the consent form. Once they have reviewed the entire consent form the study team will ask them once again if they have any questions. After all questions are answered, they can sign the consent form if they choose to participate. The patient will have the time between the discussion of the study and the day of surgery to decide if they would like to participate. This time interval is typically 1 to 2 weeks.

To avoid any coercion all subjects are offered the opportunity to talk with the treating physician or family prior to signing a consent form. Study participation has no influence on the standard of care they would otherwise receive for their disease process

VIII. Inclusion Criteria:

- Age ≥ 18 and ≤ 100 years
- Patient undergoing elective intestinal resection surgery by the colorectal surgery service at UIHC.
- Patient undergoing cystectomy surgery by the urology service at UIHC

IX. Exclusion Criteria:

- Allergies to any of the device components (ie: adhesive)
- Inability to have prototype device applied to their abdominal wall due to a condition (ie: fistulas, stomas, drains, etc).
- Patients who develop documented evidence of intraperitoneal infection or urinary tract infection within 14 days of surgery will be excluded from analysis for primary outcome (but data will undergo analysis for potential detection of secondary ileus)

X. Study Procedures:

- Potential subject is approached at preoperative visit to discuss study, if interested.
- Informed consent signed.
- Previs device is applied either in the operating room at the completion of surgery or in the recovery room.
- Time and serial number of device application will be logged into study register.
- Study team member will administer Instrument Questionnaire daily, while hospitalized, for up to 10 days.
- Study team member will remove the Previs device 10 days post-operative or at subject discharge from the hospital.
- Study team will monitor the medical record and talk with subject for 14 days to collect any data related to a possible infection (intraperitoneal or urinary tract infection).
- Study team member will contact the subject 14 days post-operative to administer Instrument Questionnaire.
- Study team will review the subject's medical record to assess for any evidence of hospital readmission within 30 days of discharge.

Table 1 Schedule of events

Event	Screening Visit	Day of Surgery (Day 1)	Day 2,3,4,5,6,7,8,9,10	14 Day Follow-Up
Informed Consent	**X**			
Medical History	**X**			
Medical Record Review		**X**	**X**	**X**
Review of inclusion/exclusion criteria to confirm subject eligibility	**X**			
Device placement		**X**		
Device removal			**X[a]**	
Instrument Questionnaire		**X**	**X**	**X**

Adverse events monitoring		**X**	**X**	**X**

a. At day 10 post-operative or discharge, whichever comes first.

XI. Possible Risks of the Study:

Risk of skin irritation where the device is placed. To minimize the risk of skin irritation, subjects will not be enrolled who have allergies to any of the device components or the adhesives that will be used. Study members will also monitor the device placement to ensure there is no irritation.

Loss of confidentiality is also a risk. To reduce risk of a loss of confidentiality, precautions will be taken to ensure privacy. The PI and study team will maintain appropriate medical and research records for this study, in compliance with ICH E6 GCP, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Research records generated in this study will be stored in file cabinets in a locked room and/or on a secure electronic database. Only authorized study team at the sites will have access to the data. Subjects will not be directly identified by name. Any identifiers that would link the subjects to the database will be stored in a password protected RedCap database. All subjects will be identified by a coded ID number.

XII. Adverse Event Reporting:

Subjects are monitored for adverse events during the study. Subjects are also educated on the risks of the study and contact phone numbers for the study team. Subjects are encouraged to contact the study personnel with any questions or concerns.

The University of Iowa requires Investigators to collect and report to the University of Iowa IRB if any of the following occur:

- An unanticipated problem involving risks to subjects or others is any event or problem that:
    1) was unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB- approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied AND

    2) suggests that the research places subjects or others (those not directly involved in the research such as research staff or family members) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized AND

    3) is related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research).

- Receipt of new information

    During the course of a study, researchers may become aware of new information that would impact a subject's decision to participate, or continue participating in the research study. For example, interim analyses of data may identify a trend which impacts the safety of subjects, or may identify early efficacy (benefit) of one of the interventions under study. In

addition, results from other research studies or changes in standards of practice or care may affect conduct of a study and would need to be communicated to research subjects.

- Noncompliance

  Noncompliance is a failure to follow the federal regulations with respect to protection of human subjects in research or failure to follow the determinations of the IRB with respect to conduct of the research as approved by the IRB.

Once per year, the IRB is required to review and approve all non-exempt research projects at intervals appropriate to the degree of risk, but not less than once a year. This is called "continuing review." Continuing review for non-exempt research is required to occur as long as the research remains active for long-term follow-up of the research subject, even when the research is permanently closed to the enrollment of new subjects and all subjects have completed all research-related interventions and to occur when the remaining research activities are limited to collection of private identifiable information.

XIII. Data Management:

The following people/agencies may have access to subject data/records:

- Study team
- Federal government regulatory agencies
- Auditing departments of the University of Iowa
- University of Iowa IRB
- Sponsor and/or its representative

To protect confidentiality, we will assign each subject a study ID. All records will be in a locked cabinet in a locked office or password protected computer system. Data and records will be managed as follows:

- Paper/hard copy records (hard copy surveys, questionnaires, case report forms, pictures, etc.) - Whenever possible, subject identifying information will be blacked out on all paper or hard copy records and replaced with the subject's unique study identifier. Paper records will be stored in a locked file cabinet in the study team's locked office.
- Electronic records (computer files, electronic databases, etc.) – All electronic data bases will only be accessed by the study team and available only with a username and password assigned to study team by the PI.
- After the completion of the study, all identifiable information will be destroyed according to the University of Iowa's IRB standards, as soon as possible.

XIV. Primary End points:

Performance of Previs device within 18 hours after surgery for predicting subsequent development of gastrointestinal impairment due to ileus.

XV. Payment for Participation:

Subjects will not receive payment for participating in this study. The study related device and study procedures will be paid for by the study.

XVI. Subject Safety:

- To minimize risks all subjects are carefully pre-screened and screened trying to identify any factors that could contribute to increased risk.
- All study procedures are completed at University of Iowa Hospitals and Clinics by a very experienced and well trained staff and monitored by the Principal Investigator.
- All confidential information is kept in locked offices and password protected computers only available to study team members.
- The participant has contact information and study team members available 24/7.

XVII. Statistical design plan:

The definition of post-operative ileus is "the presence of emesis, need for nasogastric intubation, or reversal of the diet beyond 24 hours from the completion of surgery". As the goal of the first phase of this trial is to optimize the device for predicting ileus, we will be maximizing the performance of the device through measurement of sensitivity, specificity, positive predictive value, negative predictive value, AUC, and accuracy of the device for each 10-20 patients (dependent upon the incidence of ileus in each group). The device performance will be compared to the surgeon prediction of ileus development, which will be assessed within the first 24 hours after surgery. The threshold for use in the second phase (validation phase) will be chosen to maximize sensitivity while maintaining the highest possible specificity. Ultimately, device performance will be considered successful if sensitivity higher than that of surgeons can be achieved for predicting ileus.

The study team would like to increase our enrollment plan to 225 patients. We believe that there will be a significant need for pre-optimization where the algorithm is tweaked based upon results in smaller cohorts. Enrollment of 225 patients should allow us an adequate number of cohorts to iteratively pre-optimize the algorithm prior to validation in the final cohort.