EXPAREL TRANSVERSUS ABDOMINIS PLANE BLOCK VS. INTRATHECAL ANALGESIA IN COLORECTAL SURGERY: A PROSPECTIVE RANDOMIZED TRIAL

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Study Product: Injectable liposomal bupivacaine (EXPAREL)

Protocol Number: (IRBe) 14-003143

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List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure

Study Summary

Title	EXPAREL transversus abdominis plane block vs. intrathecal analgesia in colorectal surgery: a prospective randomized trial.
Running Title	EXPAREL injection vs. intrathecal analgesia
Protocol Number	14-003143
Phase	Phase IV
Methodology	Prospective, randomized trial
Overall Study Duration	12 months
Subject Participation Duration	2-5 days
Single or Multi-Site	Single institution, multicenter
Objectives	Compare postoperative pain control between intrathecal analgesia and EXPAREL transversus abdominis plane injection. Length of stay, and complications will also be recorded.
Number of Subjects	226 total for both sites
Diagnosis and Main Inclusion Criteria	Consentable, nonpregnant adults undergoing elective colorectal surgery and enrolment in enhanced recovery program
Study Product, Dose, Route, Regimen	Liposomal injectable bupivacaine, injected once in the transversus abdominis plane bilaterally, 133mg per side.
Duration of Administration	Once
Reference therapy	Intrathecal hydromorphone
Statistical Methodology	Patients will be randomized in a 1:1 fashion. There will be two stratification factors: MIS vs. open surgery, and site (Jacksonville vs Rochester). Randomization will be performed with an online system and will use a permuted block design with varying block sizes

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

Multimodal analgesia has played a key role in decreasing postoperative pain in patients undergoing colorectal operations. Recently, its role in decreasing oral morphine equivalents (OME) has been shown to decrease length of stay (LOS) and decrease the risk of postoperative ileus (POI) at Mayo [1]. Multimodal analgesia and limiting systemic opiate use are critical components in enhanced recovery pathways. Numerous studies have assessed the best agent and mode of neuraxial blockade. Its role in decreasing narcotic use and improving POI and LOS has been well-studied [2-4]. Currently at our institution, single injection intrathecal hydromorphone analgesia is routinely used in addition to systemic, non-opiate analgesia (e.g., gabapentin, acetaminophen, non-steroidal anti-inflammatory medications).

Transversus abdominis plane (TAP) block is an alternative to neuraxial analgesia, and it has had promising results for analgesia after colorectal surgery [4-6]. A limitation of bupivacaine TAP blockade is the relatively short duration of effect, ranging on average from 6-12 hours [7]. Liposomal bupivacaine (EXPAREL) is a relatively new product currently FDA-approved for wound infiltration with an analgesic effect for 72 hours. EXPAREL has been shown to safe and effective.

1.2 Investigational Agent

EXPAREL has been approved by FDA in 2011, and has been used for wound infiltration and nerve blocks. Its analgesic effects can last up to 72 hours. It is encapsulated in vesicular liposomes, which dissolve slowly, and release bupivacaine over time, providing a longer analgesic effect than ordinary bupivacaine [8,9]. EXPAREL is supplied in one vial, containing 266mg of bupivacaine suspended in multivesicular liposomes in normal saline. (DepoFoam) [10].

1.3 Clinical Data to Date

FDA approval was based on two double blind, Phase III trials on soft tissue and orthopedic surgical models. Subsequent to that, the medication was used in another Phase III trial with patients having bunionectomies[11]. It found that EXPAREL use in 97 patients was associated with better postoperative pain, and no adverse side effects were found. Subsequently, another randomized, double blind, prospective Phase III trial was done, in patients undergoing hemorrhoidectomy [12]. The EXPAREL group (n=94) had less pain, and used less opioid medication. No adverse events were observed.

The safety profile of EXPAREL has been evaluated and in a meta-analysis, and its side effect profile has been found to be similar to bupivacaine. The most common side effects in the 800 patients in the EXPAREL group were nausea (3.3%) and constipation (2.0%). Cardiac complications were tachycardia (4%), and bradycardia (2%), which did not require treatment, and were similar to bupivacaine group. One death was reported in the 800 patients that received EXPAREL, and one in the bupivacaine group; both drugs were deemed as not the causative agents [13]

EXPAREL has been used in TAP infiltrations and has been used in two small studies totaling 37 patients. No side effects were reported, and the patients had low pain scores, with minimal narcotic use [14,15].

At our institution, EXPAREL has been used for over one year with hundreds of patients both in the Rochester and Jacksonville campuses without any side effects attributed to EXPAREL injection.

1.4 Dose Rationale and Risk/Benefits

After induction of anesthesia, the patients will receive a single injection with 133 mg of EXPAREL suspended in 20mL of injectable saline, in each side, in the transversus abdominis plane (TAP). The injection will be ultrasound guided, and performed by our interventional anesthesiologists. The risks are the same as any non-EXPAREL TAP block, which include bleeding, infection, and pain. Systemic absorption of EXPAREL is possible, but as above (section 1.3), the side effects have not been found to be any different than the use of ordinary bupivacaine.

The risks will be included in the consent form, which include arrhythmias, bleeding infection, pain, and are no different than the use of TAP Bupivacaine, which is a standard of practice in our institution.

The alternate treatment group (the control group) will receive 100 mcg hydromorphone in a single intrathecal injection, administered by our interventional anesthesiologists immediately preoperatively. This is currently used routinely in the colorectal practice, as well as other practices across the enterprise.

2 Study Objectives

Primary Objective

To assess efficacy of EXPAREL TAP blocks in improving pain scores for 48 hours postoperatively, and in reducing total oral morphine equivalents (OME) use, compared to standard Intrathecal opioid administration (IT).

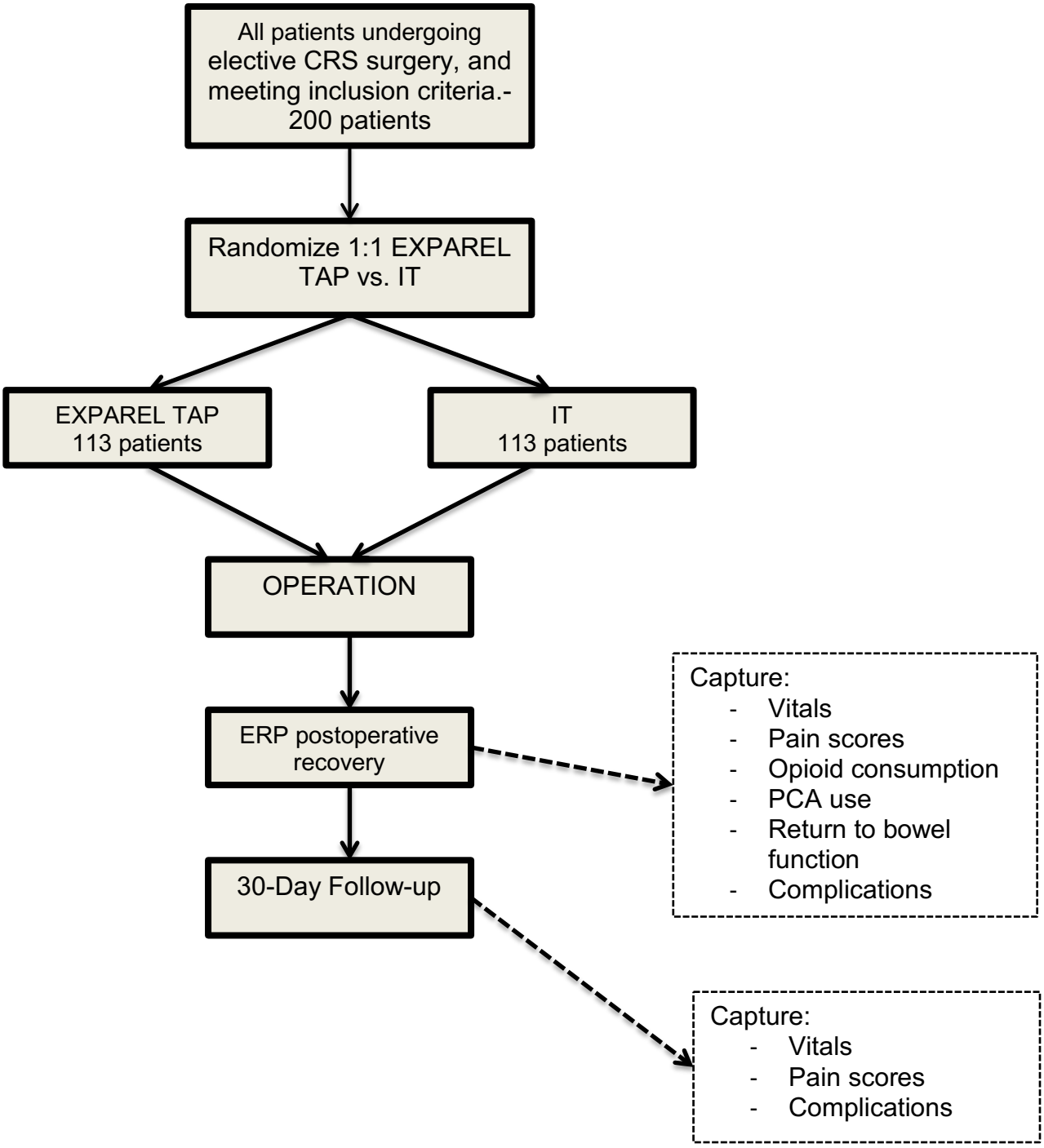
Secondary Objective

Assess the length of stay (LOS), postoperative ileus (POI) incidence, and the use of intravenous patient controlled analgesia (PCA) in patients that had EXPAREL TAP blocs compared to IT.

3 Study Design

3.1 General Design

This study is prospective, randomized trial in which EXPAREL TAP block is compared to standard IT opioid administration, in relieving postoperative pain, decreasing length of stay, and use of narcotic medication. Subjects will be screened at outpatient clinic visit appointments and interested qualified subjects will be consented and offered participation in this trial. All enrolled patients will be entered by the surgeon through written informed consent. All data will be entered in a prospective automated institutional database.


All patients undergoing elective CRS surgery, and meeting inclusion criteria.- 200 patients
Randomize 1:1 EXPAREL TAP vs. IT
EXPAREL TAP 113 patients
IT 113 patients
OPERATION
ERP postoperative recovery
30-Day Follow-up
Capture:
- Vitals
- Pain scores
- Opioid consumption
- PCA use
- Return to bowel function
- Complications
Capture:
- Vitals
- Pain scores
- Complications

3.2 Primary Study Endpoints

Primary end points include mean pain scores for 48 hours and OME use associated with IT and EXPAREL TAP.

3.3 Secondary Study Endpoints

Secondary endpoints include LOS, the incidence of POI, and use of PCA

3.4 Primary Safety Endpoints

Patients will be monitored both intraoperatively and postoperatively for any adverse events (as defined below and in section 8). Patients will be connected to a cardiac monitor intraoperatively, and until the morning of postoperative day 1 (POD1). Patient will also be connected to a continuous pulse oximeter until the morning of postoperative day 1 (POD 1). These are standard practice for the recovery units. The surgical team will assess the patient routinely twice daily, more often if necessary. Vital signs (heart rate, oxygen saturation, and blood pressure) will be captured at least four times per day, more frequently if the clinical situation dictates. In addition, patients will all have a complete blood count, and creatinine checked on POD1 routinely. None of the patients enrolled in the trial will receive any amide-type anesthetics within 72 hours after EXPAREL use.

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

- All patients undergoing elective minimally invasive or open small bowel or colorectal resections who are eligible for IT, and able to be enrolled in ERP.
- Age >18 years
- BMI <40
- Ability to understand and read English

4.2 Exclusion Criteria

- Not able or unwilling to sign consent.
- Currently pregnant or lactating.
- Patients with chronic pain, requiring daily opiate use at time of surgery.
- Patients intolerant or allergic to opiates, NSAIDS, acetaminophen or amide-type local anesthetics.
- Patients requiring emergent surgery.
- Abdominoperineal resections.
- **Any contraindications to neuraxial analgesia (coagulopathy, localized infection at the potential site of injection, pre-existing spinal canal pathology, previous spine surgery or peripheral neuropathy)**
- Patients with a diagnosis of inflammatory bowel disease.

- Patients have had or planned to have hepatic resection
- AST and/or ALT abnormal
- Renal insufficiency (creatinine clearance less than 30)
- Any patient currently receiving any anticoagulation medication other than aspirin, and/or with an INR > 1.4, as per ASRA guidelines [16].

4.3 Subject Recruitment, Enrollment and Screening

After institutional review board approval, all adult patients undergoing elective laparoscopic and open colorectal resections are considered for admittance into the trial. All enrolled patients will be entered by the surgeon through written informed consent. All patients enrolled will need to meet the inclusion idea (see section 4.1).

4.4 Subjects

4.4.1 When and How to Withdraw Subjects

Patients may withdraw from the study at any point before induction of anesthesia for their elective operation.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Patients that withdraw from the study will not have received the treatment; therefore, no data will need to be collected, other than that they were considered for enrolment.

5 Study Drug

5.1 Description

The EXPAREL solution will be housed in a transparent vial, which will appear milky-white because the solution itself is milky white.

5.2 Treatment Regimen

After induction of anesthesia, the patients will receive a single injection with 133 mg of EXPAREL in the transversus abdominis plane (TAP), on each side, suspended in 20mL of injectable saline.

5.3 Method for Assigning Subjects to Treatment Groups

All enrolled patients will be entered by the surgeon through written informed consent. Patients will be randomized 1:1 to either receive:

Group A: IT

Or

Group B: EXPAREL TAP.

There will be two stratification factors: type of surgery (MIS versus open), and site (Jacksonville versus Rochester).

5.4 Preparation and Administration of Study Drug

EXPAREL is suspended in 20 ml of injectable saline from the manufacturer (containing 266 mg of liposomal bupivacaine). An additional 20 mL of injectable saline will be used to

further dilute the drug to a total volume of 40ml. Under ultrasound guidance, 20 ml (133 mg) of the solution will be injected once in the transversus abdominis plane on each side. Thus, each side will receive 133 mg of EXPAREL suspended in 20 mL of saline.

5.5 Subject Compliance Monitoring

Patients receiving treatment will be enrolled in a prospective database. No other treatment is necessary, except the single injection before their scheduled procedure.

5.6 Prior and Concomitant Therapy

Patients may receive therapy for any conceivable condition, while enrolled in this trial, as long as the meet the inclusion criteria (section 4.1).

5.7 Packaging

Exparel solution will be packaged from the manufacturer, and will appear as a vial containing 20 ml of milky white suspension.

5.8 Masking/Blinding of Study

The study will not be blinded.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

EXPAREL is already being used throughout the enterprise, and its storage, handling, transport and disposal will not change.

5.9.2 Storage

EXPAREL is already being used throughout the enterprise, and its storage, handling, transport and disposal will not change.

5.9.3 Dispensing of Study Drug

EXPAREL is already being used throughout the enterprise, and its storage, handling, transport and disposal will not change.

5.9.4 Return or Destruction of Study Drug

EXPAREL is already being used throughout the enterprise, and its storage, handling, transport and disposal will not change.

6 Study Procedures

EXPAREL is administered only once as described in section 5.4.

Safety data will be collected on the patient for 30 days, +/- 10 days after administration of study treatment. The collection of data will be through the patient's medical record from their normal post-operative care visits to the clinic. If the patient does not return to the clinic, they patient will be contacted by phone to assess the patient for any adverse events. All adverse events are reported to the study PI.

7 Statistical Plan

7.1 Randomization

Patients will be randomized in a 1:1 fashion. There will be two stratification factors: type of surgery (MIS vs. open surgery) and site (Jacksonville versus Rochester). Randomization will be performed with an online system and will use dynamic allocation..

7.2 Sample size

The two primary endpoints of interest are pain scores over 48 hours post-surgery and the amount of narcotic medication used, standardized to OME, over 48 hours post-surgery. The pain score endpoint will be summarized as area under the curve (AUC), normalized for the total time of observation. A sample size of 100 patients per arm provides 80% power to detect an effect size of 0.40 using a two group t-test with a 0.05 two-sided significance level. The effect size is the expected difference in the mean AUCs divided by the within group standard deviation. A difference of 0.5 standard deviations in pain scores has been demonstrated to be clinically meaningful in the QOL literature. This study is adequately powered to detect this; a sample size of 100 patients in each group has 94% power to detect a difference in the mean AUC pain scores between the two groups of 0.50 standard deviations. The narcotic medication use (standardized OME) will be the cumulative use over the 48 hour period. It is also felt that a difference of 0.4 standard deviations in the mean narcotic use (standardized to OME) between the groups is clinically meaningful.

7.3 Analysis plans

Patient Population(s) for Analysis

The patient for the primary analysis will be all randomized patients who did not withdraw prior to the initiation of anesthesia. The numbers of patients that withdraw prior to undergoing surgery will be monitored for imbalances between the arms.

Primary analysis plan

The primary analysis will be a modified intent-to-treat analysis. This means it will be an analysis of all randomized patients who did not withdraw prior to surgery according to the arm to which they were randomized.

The mean pain scores over 48 hours will be summarized as the area under the curve (AUC) of the observed pain score (y-axis) plotted by the time it was measured (x-axis). The difference in mean AUCs of the two groups will be evaluated using a two-sample t-test. In addition, the cumulative narcotic use over the 48 hour period will be determined for each patient (standardized OME). The difference in mean standardized OME will be compared with a two-sample test. If the data are skewed, a two-sample t-test will be performed on the logged values of OME or a Wilcoxon rank sum test will be used on the untransformed data.A two-sided p-value will be declared statistically significant for each primary endpoint. This will mean that the overall two-sided level of significance for the trial will be 0.10.

In addition to looking at the summary of the pain scores and OME scores, we will also plot these values over time and determine whether there are differences at individual time points.

Secondary analysis plan

The mean length of stay will be compared between the two groups with a two-sample test. If there are no outliers, a two-sample t-test will be used. If there are outliers, a Wilcoxon rank sum test will be used. A chi-square test (or Fisher's exact test) will be used to compare the rates of POI, need for a PCI and post-operative hypotension.

Comparisons will be made between the randomized groups of the baseline variables (patient, disease, and surgical) to determine if there were any randomization imbalances. If imbalances are found, a secondary analysis will be done using linear regression and adding the variables that were not balanced between the groups.

Descriptive Statistics

Univariable descriptive statistics will be calculated for all variables; categorical variables will be summarized as counts (relative frequencies) and continuous variables will be summarized as mean± standard (SD) and median (min value, max value) .

Handling of Missing Data

Missing data will prompt individual review of the patient's electronic record to obtain missing variables. Analyses will be done using all patients who have the necessary data for the analysis. If the amount of missing data within an analysis is greater than 10%, imputation methods will be used and the data re-analyzed as a sensitivity analysis.

7.5 Data Collection

Data will be captured in an electronic fashion via institutional database that is already in use for the Rochester site. A REDCap database will be used to capture the information at the Jacksonville site and to capture adverse event (complication) data from both sites. The same definition of variables will be used at both sites.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization, readmission, or prolonged hospital stay; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event

An untoward or undesirable experience associated with the use of the medications used in this trial, as bellow:

- Any arrhythmia/ tachycardia/bradycardia necessitating intervention (medicine or cardioversion)
- Vertigo, tinnitus, seizure
- Any myocardial infarction
- Any site infection / hemorrhage / persistent injection site pain, neuropathy or nerve injury
- Postoperative headaches

Serious Adverse Event

Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- Death
- Life threatening adverse experience
- Hospitalization
- Inpatient, new, or prolonged; disability/incapacity
- Persistent or significant birth defect/anomaly

and/or as per protocol there may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

Other important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

For this study, the study treatment follow-up period is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event worksheet. All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified (as previously identified), the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

8.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

8.4 Unmasking/Unblinding Procedures

This study is not blinded.

8.5 Adverse Event Stopping Rule

Adverse events will be continuously monitored by the study team for patient safety. Each month, a report of the adverse events and SAEs will be generated. This report will

include the enumeration and tallies of the adverse events (and SAEs) by arm. A chi-square test (or Fisher's exact test, whichever is appropriate) will be used to compare the AE and SAE rates between the arms. If there is a statistically significant difference in SAE rates between the two arms, accrual to the trial will be temporarily suspended while the study team does a thorough evaluation of the SAEs observed. Upon a thorough review of the observed SAEs, the study team and DSMB will made a determination whether to reopen the trial with no amendments, to amend the trial and reopen, or to permanently close the trial.

The monthly SAE rate report will be sent to the DSMB Chair. This will determine whether or not a non-scheduled DSMB meeting needs to be convened prior to the 6 month DSMB review.

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.6.1 Internal Data and Safety Monitoring Board

The sponsor-investigator and participating surgeons, as well as the study coordinator will meet once monthly to review any adverse events.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records

include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Data Management

Data will be captured in an electronic fashion via institutional database that is already developed

Data Processing

Each campus will record the same data separately; all data will be combined quarterly and interim analysis will be performed.

Data Security and Confidentiality

Access to the data will be provided to only necessary persons, those that collect the data, or need to analyze the data. Data will be stored in a password-protected folder behind the Mayo firewall. All data collection and analysis will be done behind the firewall.

Data Quality Assurance

All data will be entered by appropriately trained personnel, and 1 in 50 records will be "biopsied" for correct data collection.

Data Clarification Process

Incomplete, or erroneous data will be corrected by analyzing the original patient electronic record.

9.3 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for;

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717

Whichever is longer

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

As a service to the sponsor-investigator, this study may be monitored during the conduct of the trial by staff from the Mayo Clinic Office of Research Regulatory Support. Clinical trial monitoring may include review of the study documents and data generated throughout the duration of the study to help ensure the validity and integrity of the data along with the protection of human research subjects. This will assist sponsor-investigators in complying with Food and Drug Administration regulations.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

12 Study Finances

12.1 Funding Source

This study has been approved to have study coordinator, and statistics support from the Department of Surgery for the Jacksonville campus. The Rochester campus will receive coordinator and statistics support from the Department of Surgery Rochester campus.

The medication (EXPAREL) is not a new medicine and is already being used in the colorectal surgery practice, and thus, will be billed to the patient as part of the operation.

12.2 Conflict of Interest

None.

13 Publication Plan

Subsequent to trial closure, data will be analyzed, and a manuscript will be submitted to the appropriate journal, after consensus among all the investigators.

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