

Date: Wednesday, June 5, 2019 1:08:09 PM

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## Basic Study Information

**1. \* Title of study:**

Effect of Scheduled IV Acetaminophen for Post-Operative Pain Management in Enhanced Recovery After Surgery Population- A prospective, double blinded, randomized and placebo controlled study

**2. \* Short title:**

Effect of Scheduled IV Acetaminophen for Post-Operative Pain Management in Enhanced Recovery After Surgery Population

**3. \* Brief description:**

The primary goal of this study is to assess the utility of a postoperative intravenous acetaminophen dosing schedule in minimizing postoperative pain, opioid consumption and opioid-related side effects. We also aim to study overall patient satisfaction and cost-effectiveness (direct and indirect costs) of this regimen as part of ERAS protocol at a large tertiary medical center.

**4. \* What kind of study is this?**

Single-site study

**5. \* Will an external IRB act as the IRB of record for this study?**

Yes  No

**6. \* Local principal investigator:**

Kathirvel Subramaniam

**7. \* Does the local principal investigator have a financial interest related to this research?**

Yes  No

**8. \* Attach the protocol:**

- **Sponsor/Multicenter/Investigator-initiated protocol**
- **Coordinating Center supplement**
- **Emergency Use Consent/ Protocol/ FDA Form 3926**
- **Exempt Application form**

Document Category Date Modified Document History

There are no items to display

View: Pitt SF: Funding Sources (not integrated with Grants)

# Funding Sources

**1. \* Indicate all sources of support:**

External funding

**2. \* Identify each organization supplying funding for the study:**

Funding Source	Sponsor's Funding ID	Grants Office ID	Attachments
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Mallinckrodt Pharmaceuticals

## Study Team Members

1. \* Identify each person involved in the design, conduct, or reporting of the research (includes PI):

Name	Roles	Affiliation	Involved in Consent	Qualifications
Michael Boisen	Co-investigator	Pitt faculty	yes	Michael Boisen, MD is an attending anesthesiologist at UPMC Presbyterian.
Charles Boucek	Co-investigator	Pitt faculty	yes	Boucek Charles MD is clinical anesthesiologist at UPMC Montefiore
Tomas Drabek	Co-investigator	Pitt faculty	yes	Drabek Tomas MD is a clinical anesthesiologist at UPMC Montefiore
Stephen Esper	Co-investigator	Pitt faculty	yes	Stephen A. Esper, MD is an attending anesthesiologist at UPMC Presbyterian.
John Hache	Co-investigator	Pitt faculty	yes	Hache John MD is a clinical anesthesiologist at UPMC Montefiore
Ibtesam Hilmi	Co-investigator	Pitt faculty	yes	Hilmi Ibtesam MD is a clinical anesthesiologist at UPMC Montefiore
Jennifer Holder-Murray	Co-investigator	Pitt faculty	yes	Jennifer Holder-Murray, MD is a colorectal surgeon at UPMC Presbyterian
Caroline Kostishack	Key Personnel / Support Staff Secondary Study Coordinator	UPP/UPMC staff	yes	Caroline Stehle (nee Kostishack) is a clinical research associate in the Clinical Trials Program
Kushi Mallikarjun	Key Personnel / Support Staff	UPP/UPMC staff	yes	Kushi Mallikarjun is a clinical research associate in the Clinical Trials Program
David Medich	Co-investigator	Pitt faculty	yes	David Medich, MD is a colorectal surgeon at UPMC Presbyterian
Amy Monroe	Primary Study Coordinator	Pitt staff	yes	Amy Monroe is the clinical trials program manager

Name	Roles	Affiliation	Involved in Consent	Qualifications
Stephanie Nam	Secondary Study Coordinator	UPP/UPMC staff	yes	Stephanie Nam is a clinical research coordinator in the Clinical Trials Program
Matthew Neal	Co-investigator	Pitt faculty	yes	Matthew Neal, MD is a general/trauma surgeon at UPMC Presbyterian
Raymond Planinsic	Co-investigator	Pitt faculty	yes	Raymond Planinsic MD is Director of Transplant Anesthesia and anesthesiologist at UPMC Montefiore
Tetsuro Sakai	Co-investigator	Pitt faculty	yes	Tetsuro Sakai MD is a clinical anesthesiologist at UPMC Montefiore
Javier Salgado Pogacnik	Co-investigator	Pitt faculty	yes	Javier Salgado Pogacnik, MD is a colorectal surgeon at UPMC Presbyterian
Kathirvel Subramaniam	Principal Investigator	Pitt faculty	yes	Kathirvel Subramaniam, MD, Associate Professor of Anesthesiology, is an attending anesthesiologist at UPMC Presbyterian. He has been a co-investigato... <a href="#">view all</a>
Brian Zuckerbraun	Co-investigator	Pitt faculty	yes	Brian Zuckerbraun, MD is a general/trauma surgeon at UPMC Presbyterian

**2. External team member information: (Address all study team members in item 1. above and leave this section blank)**

Name Description

There are no items to display

**3. Have you, Kathirvel Subramaniam, verified that all members of the research team have the appropriate expertise, credentials, training, and if applicable, child clearances and/or hospital privileges to perform those research procedures that are their responsibility as outlined in the IRB application?**

\*  Yes  No

## Study Scope

Check all that apply

### 1. \* Will this study actively recruit any of the following populations?

- Adults with impaired decision-making capacity
- Children (under the applicable law of the jurisdiction in which the research will be conducted (<18 years for PA))
- Children who are Wards of the State
- Employees of the University of Pittsburgh/UPMC
- Medical Students of University of Pittsburgh as primary research group
- Students of the University of Pittsburgh
- Neonates of uncertain viability
- Non-viable neonates
- Non-English speakers
- Nursing home patients in the state of Pennsylvania
- Pregnant women
- Prisoners
- N/A

### 2. \* Will any Waivers be requested?

- Waiver/Alteration of Consent
- Waiver to Document Consent
- Waiver/Alteration of HIPAA
- Exception from consent for emergency research
- N/A

### 3. \* Will this study involve any of the following?

- Specimens
- Honest Broker to provide data/specimens
- Return of Results to Subjects or Others
- Fetal tissue
- N/A

### 4. \* Will Protected Health Information be collected?

- Pitt medical records

- UPMC medical records
- Other Institutions' medical records
- N/A

**5. \* Other Requests?**

- Deception (if not Exempt, also requires Waiver/Alteration of Consent)
- Emergency Use / Single Patient Expanded Access
- Placebo Arm
- Withdraw from usual care
- N/A

**6. \* Determining Scientific Review:**

Department Scientific Review (DOD requires departmental review)

**\* Choose the appropriate organization to conduct the scientific review:**

[U of Pgh | School of Medicine | Anesthesiology](#)

**7. \* Has this study (or substantially similar study) been previously disapproved by the Pitt IRB or, to your knowledge, by any other IRB?**

Yes  No

*Review the [HRPO policy](#), if participating in research at the VA Pittsburgh Healthcare System or using funding from the VA*

**8. \* Does the study use an approved drug or biologic, use an unapproved drug or biologic, or use a food or dietary supplement to diagnose, cure, treat, or mitigate a disease or condition?**

Yes  No

**9. \* Does the study evaluate the safety or effectiveness of a device?**

Yes  No

**10. \* Is this application being submitted to convert an approved study from OSIRIS to PittPRO? ([Tip Sheet](#))**

Yes  No

*Download the [OSIRIS Transition Continuing Review form](#), complete and upload below. If you need to attach any additional documents (e.g., data and safety monitoring reports), upload in the Local Supporting Documents page and note the Renewal on the form.*

**OSIRIS Transition Continuing Review form:**

HRP-720 - OSIRIS.Conversion.ContinuingReview\_Version\_0.01.docx(0.02)

**\* OSIRIS ID**  
PRO17050418



## Research Sites

**1. Choose all sites that apply:**

UPMC

**\* Select the UPMC sites where research will be conducted:**

Presbyterian

**2. Describe the availability of resources and the adequacy of the facilities to conduct this study:**

UPMC Presbyterian is a hospital with an Acute Interventional Perioperative Pain Service (AIPPS). The anesthesiologists here routinely participate in clinical trials and various other types of clinical research, are well acclimated to conducting clinical research with respect to good clinical practice. There are sufficient resources of manpower and supplies to conduct the study

# Drugs

1. \* List all drugs, biologics, foods, and dietary supplements to be used in the study:

Generic Name	Brand Name	Attachment Name
<a href="#">View</a> Acetaminophen	Tylenol	<a href="#">Acetaminophen Injection FDA label.pdf</a>

2. \* Will the study be conducted under an investigational new drug application (IND) or radiation human subcommittee (HUSC)?

Yes  No

3. Attach files: (such as IND, HUSC, or other information that was not attached for a specific drug)

Document	Category	Date Modified	Document History
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There are no items to display

4. \* Describe your plan to store, handle, and administer drugs so that they will be used only on subjects and be used only by authorized investigators:

Both study drug (IV Tylenol) and placebo will be stored and dispensed by Investigational Drug Services (IDS) pharmacy. Drug from IDS will be affixed with subject label to ensure proper dispensing on the nursing unit.

5. \* Do you plan to utilize the UPMC Investigational Drug Service (IDS) to dispense the drug?

Yes  No

Click **Continue** as this page was intentionally left blank.

## Study Aims

**1. \* Describe the purpose, specific aims, or objectives and state the hypotheses to be tested:**

Number of patients with unsatisfactory pain relief defined as average numerical rating scale (NRS) more than 5 with or without requirement of IVPCA for pain relief during the first 48 hours postoperative period will be compared between the two groups and form the primary outcome for the study

The specific aims of this study are to:

1. Assess the efficacy of scheduled intravenous acetaminophen dosing as part of an enhanced recovery anesthetic protocol in improving postoperative pain control (patient controlled analgesia requirement, pain scores and total intravenous opioid consumption) in the postoperative period as compared to a placebo control.
2. Assess the ability of systematically administered intravenous acetaminophen in the immediate postoperative period to reduce opioid-related side effects
3. Evaluate overall patient satisfaction and outcomes after major abdominal surgery with IV acetaminophen added to ERAS protocol.
4. Assess the cost-effectiveness of IV acetaminophen in ERAS protocols for major abdominal surgery (direct and indirect costs)

**2. \* Describe the relevant prior experience and gaps in current knowledge including preliminary data. Provide for the scientific or scholarly background for, rationale for, and significance of the research based on existing literature and how it will add to existing knowledge:**

Several recent studies explored the role of intravenous acetaminophen as an adjuvant for postoperative analgesia after Food and Drug Administration approved its use in 2010. IV Acetaminophen use as analgesic has been studied in orthopedic surgery, dental surgery, abdominal surgery, cardiac surgery, abdominal hysterectomy and other major surgical procedures (4-11). Several studies have found significant reductions in opioid requirements, lengths of stay, and overall complication rates for surgical patients having received IV acetaminophen (12,13,14,15). Among pain outcome measures, the use of acetaminophen improves pain scores but the evidence for reduction in opioid consumption is equivocal (10,16). Very few clinical trials reported no improvement with pain related outcomes (17-19). The difference in results between studies can be explained by retrospective study design, small sample size, varying dose regimens for acetaminophen, and not reporting all patient outcomes.

Review of literature on the effect of adding acetaminophen to patients undergoing major abdominal surgical procedures revealed few clinical trials. Bameshki et al have shown that IV paracetamol decreased morphine consumption by 32% and improved alertness after gastrectomy (n=90). No decrease in opioid related adverse events were seen with IV paracetamol (20). Strode et al (n=34) studied patients who underwent laparoscopic sleeve gastrectomy and found that IV paracetamol decreased subjective pain but did not decrease narcotic use (21). In patients undergoing bariatric surgery (N=88), Wang et al (19) were not able to demonstrate the beneficial effects of adding acetaminophen on postoperative analgesia and acetaminophen group had higher opioid consumption while several other groups have shown positive effects of IV acetaminophen (22,23). Ziolkowski et al, studied the patients undergoing bowel surgery with IV acetaminophen therapy and compared with historical control. Time to ambulation was significantly shortened in patients received IV acetaminophen (24). Wininger et al (25) conducted a prospective, multi-center, placebo controlled clinical trial after laparoscopic abdominal surgery and have shown that two IV acetaminophen dose regimens (650 mg every 4 hours and 1g every 6 hours) produced better pain relief compared to placebo. However, the results of many of these existing studies cannot be generalized to patients undergoing large abdominal or colorectal procedures with current ERAS protocols utilizing mainly non-narcotic multimodal analgesic regimens.

Apfel et al (26) conducted a systematic review of the clinical trials evaluating the effect of acetaminophen on PONV. They included 30 studies with 2364 patients (1223 in the acetaminophen group, 1141 in the placebo group). The relative risk (95% confidence interval) was 0.73 (0.60-0.88) for nausea and 0.63 (0.45-0.88) for vomiting.

Interestingly, acetaminophen was effective only when it was given before the start of the surgery or before arrival in post-anesthesia care unit but not when given after the onset of pain. It can be concluded that Acetaminophen reduces PONV primarily by reducing pain.

4. Hansen RN, Pham A, Strassels SA, Balaban S, Wan GJ. Comparative Analysis of Length of Stay and Inpatient Costs for Orthopedic Surgery Patients Treated with IV Acetaminophen and IV Opioids vs. IV Opioids Alone for Post-Operative Pain. *Adv Ther.* 2016 Jul 16.

5. Bollinger AJ, Butler PD, Nies MS et al. Is Scheduled Intravenous Acetaminophen Effective in the Pain Management Protocol of Geriatric Hip Fractures? *Geriatr Orthop Surg Rehabil.* 2015 Sep;6(3):202-8.

6. Herring BO, Ader S, Maldonado A et al. Impact of intravenous acetaminophen on

reducing opioid use after hysterectomy. *Pharmacotherapy* 2014;34(12 Pt 2):27S–33S

7. Jokela, R., Ahonen, J., Seitsonen, E. et al, The influence of ondansetron on the analgesic effect of acetaminophen after laparoscopic hysterectomy. *Clin Pharmacol Ther.* 2010;87:672–678.
8. Gonzalez A, Ziemann-Gimmel P. The role of multimodal analgesia in bariatric surgery: A review of clinical data and case-based presentations featuring OFIRMEV® (acetaminophen) injection. *Surgical Pain Management.* 2014;11(5): A2-11.
9. Pettersson PH, Jakobsson J, Owall A. Intravenous acetaminophen reduced the use of opioids compared with oral administration after coronary artery bypass grafting. *J Cardiothorac Vasc Anesth.* 2005;19(3):306-9.
10. Mamoun NF, Lin P, Zimmerman NM, Mascha EJ, Mick SL, Insler SR, Sessler DI, Duncan AE. Intravenous acetaminophen analgesia after cardiac surgery: A randomized, blinded, controlled superiority trial. *J Thorac Cardiovasc Surg.* 2016 May 5. pii: S0022-5223(16)30292-6.
11. Douzjian DJ, Kulik A. Old Drug, New Route: A Systematic Review of Intravenous Acetaminophen After Adult Cardiac Surgery. *J Cardiothorac Vasc Anesth.* 2016 Mar 16. pii: S1053-0770(16)00265-2.
12. Thiele RH, Rea KM, Turrentine FE, et al. Standardization of care: impact of an enhanced recovery protocol on length of stay, complications, and direct costs after colorectal surgery. *Standardization of Care in Colorectal Surg.* 2015;220:430–43.
13. Doleman B, Read D, Lund JN, et al. Preventive acetaminophen reduces postoperative opioid consumption, vomiting, and pain scores after surgery: systematic review and meta-analysis. *Reg Anesth and Pain Med.* 2015;40:706-12.
14. Remy, C., Marret, E., Bonnet, F. Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. *Br J Anaesth.* 2005;94:505–513.
15. Marcario A, Royal MA. A literature review of randomized clinical trials of intravenous acetaminophen for acute postoperative pain. *Pain Pract* 2011;11:290-296
16. Cakan, T., Inan, N., Culhaoglu, S. et al, Intravenous paracetamol improves the quality of postoperative analgesia but does not decrease narcotic requirements. *J*

Neurosurg Anesthesiol. 2008;20:169–173.

17. Brett CN, Barnett SG, Pearson J. Postoperative plasma paracetamol levels following oral or intravenous paracetamol administration: a double-blind randomized controlled trial. *Anaesth Intensive Care*. 2012; 40:166-71.

18. Fenlon S, Collyer J, Giles J, et al. Oral vs intravenous paracetamol for lower third molar extractions under general anaesthesia: is oral administration inferior? *Br J Anaesth*. 2013;110:432-7.

19. Wang S, Saha R, Shah N, Hanna A, DeMuro J, Calixte R, Brathwaite C. Effect of Intravenous Acetaminophen on Postoperative Opioid Use in Bariatric Surgery Patients. *P T*. 2015 Dec;40(12):847-50.

20. Bameshki A, Peivandi Yazdi A, Sheybani S, Rezaei Boroujerdi H, Taghavi Gilani M. The Assessment of Addition of Either Intravenous Paracetamol or Diclofenac Suppositories to Patient-Controlled Morphine Analgesia for Postgastrectomy Pain Control. *Anesth Pain Med*. 2015 Oct 10;5(5):e29688.

21. Strode MA, Sherman W, Mangieri CW, Bland CM, Sparks PJ, Faler BJ, Prasad BM, Choi YU. Randomized trial of OFIRMEV versus placebo for pain management after laparoscopic sleeve gastrectomy. *Surg Obes Relat Dis*. 2016 May;12(4):772-7.

22. Saurabh S, Smith JK, Pedersen M, Jose P, Nau P, Samuel I. Scheduled intravenous acetaminophen reduces postoperative narcotic analgesic demand and requirement after laparoscopic Roux-en-Y gastric bypass. *Surg Obes Relat Dis*. 2015 Mar-Apr;11(2):424-30. doi: 10.1016/j.soard.2014.09.017. Epub 2014 Sep 30. PubMed PMID: 25614351.

23. Song K, Melroy MJ, Whipple OC. Optimizing multimodal analgesia with intravenous acetaminophen and opioids in postoperative bariatric patients. *Pharmacotherapy*. 2014 Dec;34 Suppl 1:14S-21S. doi: 10.1002/phar.1517.

24. Ziolkowski K, Kaufman J, Jambunathan J, Berge J, Menet L, Chappy S, Messerschmidt M. The Clinical Use of Intravenous Acetaminophen Postoperatively on Patients Who Have Undergone Bowel Surgery. *AORN J*. 2015 Nov;102(5):515.e1

25. Winger SJ, Miller H, Minkowitz HS, Royal MA, Ang RY, Breitmeyer JB, Singla NK. A randomized, double-blind, placebo-controlled, multicenter, repeat-dose

study of two intravenous acetaminophen dosing regimens for the treatment of pain after abdominal laparoscopic surgery. *Clin Ther.* 2010 Dec;32(14):2348-69. 515.e10.

26. Apfel CC, Turan A, Souza K, Pergolizzi J, Hornuss C. Intravenous acetaminophen reduces postoperative nausea and vomiting: a systematic review and meta-analysis. *Pain.* 2013 May;154(5):677-89.

Both oral and intravenous acetaminophen preparations have been shown to be useful adjuvants in multimodal analgesia. Intravenous acetaminophen has been of interest for its utility in post-surgical patients, who have not yet been cleared for oral intake. Intravenous acetaminophen should also be preferred over oral acetaminophen in patients after major abdominal surgery where absorption of medications given through oral route is erratic. Although the efficacy of intravenous acetaminophen as a postoperative pain adjunct is known, its exact role in ERAS protocols and non-narcotic multimodal analgesic regimens for major abdominal surgery has not been studied in randomized clinical trials to define its efficacy.

Clinical trials examining IV acetaminophen did not always find a reduction in opioid related side effects. This includes a recently published study by Mamoun et al (10), who has demonstrated superior pain relief (decreased pain scores) with IV Acetaminophen compared to placebo after elective cardiac surgery but also could not demonstrate a significant reduction in opioid consumption and opioid related adverse events. Failure to demonstrate an effect on opioid related side effects such as nausea and vomiting could be related to the fact that the studies were not adequately powered for reduction in adverse events.

Acetaminophen is viewed as an integral component of ERAS multimodal analgesic regimen and a well-conducted randomized prospective clinical trial is required to establish the efficacy and safety of each and every individual components of ERAS multimodal analgesic protocols. In addition, clinical trials should report all possible outcomes related to particular type of surgery. In abdominal surgery population, apart from improvement in pain outcomes, time to ambulation, time to bowel movement, time to oral intake, time to discharge, need for critical care admission, length of hospital stay, adverse events, complications (anastomotic leaks, re-explorations) and readmissions should all be reported to claim a successful clinical study.

10. Mamoun NF, Lin P, Zimmerman NM, Mascha EJ, Mick SL, Insler SR, Sessler DI, Duncan AE. Intravenous acetaminophen analgesia after cardiac surgery: A randomized, blinded, controlled superiority trial. *J Thorac Cardiovasc Surg.* 2016 May 5. pii: S0022-5223(16)30292-6.





## Recruitment Methods

**\* Will you be recruiting individuals for participation in this study?**

Yes  No

**1. \* Describe who will be recruiting individuals for participation for this study:**

Principal Investigator and Co-Investigators along with study coordinator and research associates will recruit individuals for participation in the study.

**2. \* Select all methods to be used for recruitment:**

Directly approaching potential subjects (in-person)

**3. \* Provide details on your recruitment methods:**

Potential subjects will be identified through the review of the medical records in order to exclude patients with clear and certain exclusion criteria.

Patients will be provided information about the study in preoperative clinic, surgical clinic if they are outpatients. If patients are inpatients, they will be given information about the study few days before the scheduled procedure. The patient will be urged to take as long as necessary to decide whether or not to participate.

The investigator anesthesiologist then will see the patient prior to surgery and discuss the consent form that was previously provided to the patient, including potential risks and benefits associated with the study. At the day of the surgery, subjects will be asked again if they are still interested in participating in the study and at that time the physician investigator will review the consent and obtain consent at that time.

All questions will be addressed and it will be made clear that the patient may withdraw from the study at any time. Investigator physician will sign the informed consent with the patient prior to beginning of any study procedures.

**4. \* Describe all compensation/incentives offered to participants and timing of these offers:**

Patients are not compensated for this study

**5. Recruitment materials:** (attach all material to be seen or heard by subjects, including advertisements and scripts)

Document	Category	Date Modified	Document History
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There are no items to display

## Study Design

- 1. Total number of subjects to be enrolled at this site (enter -1 for chart reviews, banking, registries):**

182

- 2. Describe and explain the study design:**

single-center prospective randomized double-blinded placebo-controlled trial

- 3. Describe the primary and secondary study endpoints:**

Number of patients with unsatisfactory pain relief defined as average numerical rating scale (NRS) more than 5 with or without requirement of IVPCA for pain relief during the first 48 hours postoperative period will be compared between the two groups and form the primary outcome for the study.

Secondary outcome measures will include time to readiness for discharge from PACU, time to bowel movement, time to oral intake (liquid and regular diet), time to ambulation, time to hospital discharge, intensive care unit (ICU) admission, readmission to the hospital, percentage of patients readmitted because of pain related issues, overall patient satisfaction, patient satisfaction relating to pain management, and cost analyses

- 4. Provide a description of the following study timelines:**

**Duration of an individual subject's active participation:**

30 days

**Duration anticipated to enroll all subjects:**

1 year

**Estimated date for the investigator to complete this study (complete primary analyses):**

10/31/2019

- 5. List the inclusion criteria:**

Elective colorectal, pancreatic, and other major (open or laparoscopic) abdominal procedure (gastric, abdominal wall hernias, separation of parts, etc.) as per our institution's enhanced recovery after surgery (ERAS) anesthetic protocol.

Patients over 18 years of age

Both female and male genders

All races

**6. List the exclusion criteria:**

Patient refusal

Documented allergy to acetaminophen

Chronic malnutrition

Chronic alcoholism

Severe hypovolemia

Preoperative renal insufficiency (creatinine clearance < 30 ml/min) or hemodialysis

History of active liver disease or hepatic impairment

Chronic pain condition that required daily preoperative opioid administration

Pregnancy or positive urine pregnancy test in women of child bearing age

Pre-existing dementia and/or other neuropsychiatric conditions impeding accurate assessment of pain scores or other study measures

Patients taking Isoniazid and warfarin

**7. Will children or any gender, racial or ethnic subgroups be explicitly excluded from participation?**

Yes  No

**\* Identify the subgroups and provide a justification:**

Presbyterian/Montefiore Hospitals serve an adult population

**8. Describe the power analysis used and cite your method of statistical analysis. If a power analysis is not possible, thoroughly justify the sample size required for the study, including appropriate literature citation (alternatively provide page reference in attached protocol):**

Calculation of sample size was done based on the percentage of ERAS population with unsatisfactory pain relief defined as average numerical rating scale (NRS) more than 5 with or without requirement of IVPCA for pain relief during the first 48 hours postoperative period. Based on retrospective review of our own patient's medical records, the incidence of unsatisfactory pain relief happens in 50% of ERAS abdominal surgical patients. The investigators have determined an absolute reduction in the incidence of patients having unsatisfactory pain relief by 25% to be clinically meaningful for any intervention. In order to detect this difference with 90% power (assuming  $\alpha=0.05$ ), a total of 77 patients per group need to be studied. With an expected 15% drop-out rate, we plan to study 182 patients total into the study but the study will be terminated at enrollment of 154 evaluable patients. Such a large sample

size will also be expected to provide enough power for evaluation of secondary outcomes like opioid related side effects (PONV).

## Research Activities

- 1. \* Provide a detailed description of all research activities (including screening and follow-up procedures) that will be performed for the purpose of this research study. This description of activities should be complete and of sufficient detail to permit an assessment of associated risks.**

After the patients sign an informed consent form, they will be enrolled into the study. Patients will be randomized to either the Acetaminophen group (intervention group) of 91 subjects, or the placebo group (control group) of 91 subjects using a sealed envelope containing a random computer-generated number. The patient will also be administered a Intensive Care Delirium Screening Checklist (ICDSC) to assess baseline delirium score. Women of child bearing age group will also receive a urine pregnancy test prior to receiving any study medication.

In addition to receiving multimodal analgesia in accordance with the institution's current ERAS protocol, the interventional group will receive 1 gram intravenous acetaminophen at the start of wound closure to be repeated every 6 hours for 48 hours postoperatively.

Likewise, the control group will also receive multimodal analgesia in keeping with the ERAS protocol; however, these patients will not receive IV acetaminophen at the start of wound closure and will be given an intravenous placebo at wound closure and every 6 hours for 48 hours postoperatively. Placebo is normal saline.

Intraoperative medications for ERAS protocols are subject to changes based on the drug shortages and availability and the changes will be applicable to both groups of patients. Changes to the medications will be noted

For both groups, the IV acetaminophen/placebo will be administered by the anesthesia team at wound closure, and by the patient-assigned clinician post-operatively throughout the duration of the study. The patient, anesthesiologist, nurses and research staff are all blinded to which treatment the subject receives. The only unblinded party are the pharmacists who will randomize the patient and prepare the drug. Unblinding can occur for any patient-safety related issue.

Number of patients with unsatisfactory pain relief defined as average numerical rating scale (NRS) more than 5 with or without requirement of IVPCA for pain relief during the first 48 hours postoperative period will be compared between the two groups and form the primary outcome for the study.

Postoperative pain intensity will be measured by NRS with 0- being no pain and 10- being maximum pain and the analgesic efficacy in both groups will also be evaluated by the amount of total narcotic consumption (measured with IV morphine equivalent doses of analgesics used to provide pain relief). Pain scores and narcotic consumption will be assessed both in the post anesthesia care unit (PACU) as well as on floor following PACU discharge. In the PACU, total IV hydromorphone consumption will be measured and pain scores will be recorded every thirty minutes until discharge to the floor. Readiness to discharge from PACU will be noted. After PACU discharge, a pain score will be obtained upon admission to the floor and thereafter every four hours for first 24-hour post-surgery, then every six hours until 48 hours postoperatively and then every twelve hours until 72 hours postoperatively. Rescue analgesia will be given if the pain NRS score is more than 4. If the patient can take oral medications, PO oxycodone 5-10 mg will be given.

If the patient cannot take oral medications or if the pain is not responsive to oral oxycodone, 'acute pain management protocol' is initiated. IV hydromorphone 0.5 mg is administered as rescue analgesic. IV ketorolac 15-30 mg can also be given for pain relief with clearance from surgical team. If the pain is refractory (NRS > 4) to 3 doses of IV hydromorphone in 8 hours, IV Ketorolac and increase in oral oxycodone dose, patient controlled analgesia with IV Hydromorphone will be offered. Time to patient-controlled analgesia (PCA) initiation on the floor, total duration of IVPCA use and total PCA hydromorphone consumption over the first 48-hour postoperative period will be noted.

Standard opioid conversion table will be used to convert the oral and IV narcotic utilized by the patients to IV morphine equivalent doses (MED) for analysis purposes. Time to patient-controlled analgesia (PCA) initiation on the floor will also be measured, as well as total PCA hydromorphone consumption over the 48-hour postoperative period.

Secondary outcome measures will include time to readiness for discharge from PACU, time to bowel movement, time to oral intake (liquid and regular diet), time to ambulation, time to hospital discharge, intensive care unit (ICU) admission, readmission to the hospital, percentage of patients readmitted because of pain related issues, overall patient satisfaction, patient satisfaction relating to pain management, and cost analyses.

Overall patient satisfaction and satisfaction of pain management during hospitalization will be measured by a numerical rating scale with 0- worst satisfaction and 10 being the best satisfaction. The patient satisfaction test will be administered by a member of the



research team.

For both groups, investigators will use Intensive Care Delirium Screening Checklist (ICDSC) to evaluate postoperative delirium at baseline and then every 24 hours for 72 hours after surgery (supplemental attachment).

Post-operative nausea and/or vomiting will be evaluated by nausea score (0-10), collected at the same time as the ICDSC scale (every 24 hours for 72 hours post-surgery). Frequency of emesis and rescue antiemetic requirement will be collected per the institution's standard of care and transcribed from the medical record by research staff.

Adverse events related neuraxial opioids such as pruritus, respiratory depression and urinary retention will be noted. We will also evaluate operative or anesthetic complications, organ morbidity (e.g., pneumonia, renal failure, stroke, cognitive dysfunction, and cardiac failure), bowel complications (prolonged ileus, anastomotic leak, abdominal sepsis) and mortality between the two groups.

Patient's overall health at 30 days after discharge will be evaluated by SF-12 health survey, which will be administered via phone call by the research staff (supplemental attached).

**2. Upload a copy of all materials used to collect data about subjects: (Attach all surveys, interview/focus group scripts, and data collection forms except for case report forms, SCID or KSADS):**

Document	Category	Date Modified	Document History
<a href="#">View SF-12.docx(0.01)</a>	Data Collection	4/16/2019	<a href="#">History</a>
<a href="#">View ICDSC.pdf(0.01)</a>	Data Collection	4/16/2019	<a href="#">History</a>

**3. \* Will blood samples be obtained for research purposes?**

Yes  No

## Consent Process

*Enter N/A in response to the following questions if a Waiver of Consent is requested for all research activities or if no subjects are being enrolled.*

**1. \* Indicate where the consent process will take place and at what point consent will be obtained:**

Patients will be provided information about the study in preoperative clinic, surgical clinic if they are outpatients. If patients are inpatients, they will be given information about the study few days before the scheduled procedure. The patient will be urged to take as long as necessary to decide whether or not to participate.

The investigator anesthesiologist then will see the patient prior to surgery and discuss the consent form that was previously provided to the patient, including potential risks and benefits associated with the study. At the day of the surgery, subjects will be asked again if they are still interested in participating in the study and at that time the physician investigator will review the consent and obtain consent at that time.

All questions will be addressed and it will be made clear that the patient may withdraw from the study at any time. Investigator physician will sign the informed consent with the patient prior to beginning of any study procedures

**2. \* Describe the steps that will be taken to minimize coercion and undue influence, including assurance that there is sufficient time for subjects to make an informed decision:**

In order to minimize the possibility of coercion or undue influence, the patients will be first informed that the choice of participation in the study is totally voluntarily in nature, and they will receive the standard of care when they decide not to participate in the study. Prospective patients will be encouraged to ask questions and to discuss the study with others during the consent process. Then, they will be assured that after participation in the study, they will receive either IV Tylenol or placebo in a randomized fashion if they participate in the study.

**3. For studies that involve multiple visits, describe the process to ensure ongoing consent:**

At the post-op 30 day phone call, subjects will be asked if they have any questions and will be reminded about the goals and objectives of the study. The subjects will also be

reminded that they can withdraw from the study at any time and do not have to answer the questionnaire.

**4. \* Steps to be taken to ensure the subjects' understanding:**

Individuals will be provided with full explanation of study-related goals and procedures. Questions will be answered from the patient as well as their family members as necessary. Patients will be given as much time as necessary to read the consent form and ask questions.

**5. \* Are you requesting an exception to the IRB policy related to the informed consent process:**

Yes  No

# Consent Forms

## 1. Consent Forms:

	Document	Category	Date Modified	Document History
<a href="#">View</a>	<a href="#">ICF without footer 4.30.19.docx(0.02)</a>	Consent Form	4/30/2019	<a href="#">History</a>

Refer to the following templates and instructional documents:

- Guidance - [Consent Wording](#)
- Template - Consent Document - [Short Form](#)
- HRP-090 - SOP - [Informed Consent Process for Research](#)
- HRP-091 - SOP - [Written Documentation of Consent](#)

## Waiver/Alteration of Consent

- 1. \* Select all options that apply to the request to waive the requirement to obtain informed consent:**

Review of identifiable medical records

*General Requirements: The Federal Policy (45 CFR 46.116 (d)) as well as guidance issued by the FDA requires the following criteria to be met for a waiver or alteration of consent to be approved with one exception. The FDA does not include a biospecimen provision (Item #4 below). You **MUST** provide a justification addressing how each of the criterion are met for each option chosen in Item #1.*

- 2. \* The research involves no more than minimal risk to the subjects;**

To enroll patients into the study, medical records of potential subjects will be reviewed. The medical record will be reviewed and if the patient is eligible, further consent process will be followed. If the patient is not eligible, patient's data will not be stored in the study database except the number of patients screened will be entered and stored within the UPMC firewall in a password protected file and drive

- 3. \* The waiver or alteration will not adversely affect the rights and welfare of the subjects;**

Medical record review and further eligibility into the study will not affect the patient's right to any standard therapy and welfare of subjects in anyway. If the patient is not eligible, they will receive standard perioperative therapy by anesthesia/ surgery and patient care team. Dr Subramaniam and other anesthesia team members of the study may provide anesthesia/surgical care even if the patient's are ineligible for the study and follow the standard of care

- 4. If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format (enter N/A for FDA regulated studies);**

Identification of potential subjects can be done by speaking with all potential subjects or by selectively identifying potentially eligible patients through medical record review. Medical record review will avoid speaking with all patients who are already under stress of undergoing cardiac surgery. But any medical record review by a physician not directly involved in the patient care requires waiver of consent, Without this waiver, we cannot identify potential research subjects

**5. \* The research could not practicably be carried out without the waiver or alteration;**

We cannot feasibility approach every patient who is having surgery without determining if they qualify beforehand

**6. \* Whenever appropriate, the subjects will be provided with additional pertinent information after participation;**

We will not acquire any information that will be pertinent to the participant's care since this Waiver only applies to the this limited recruitment procedure. Only eligibility criteria (inclusion and exclusion criteria) of the patients will be reviewed. No other personnel or individual patient care information will be reviewed

**7. \* Under what circumstances (if any) will you obtain consent from some of these subjects:**

A preliminary and limited assessment of patients medical charts will occur just to exclude patients with clear and certain exclusion criteria. Medical records will be reviewed under a waiver of consent for all subjects. They will provide informed consent prior to enrolling in the study.

## Medical Records

1. You are required to submit this study to the Research Informatics Office, Health Record Research Request (R3). Per UPMC Policy HS-RS0005, all research projects that access or involve UPMC electronic protected health information (e-PHI) must be submitted to R3, with the exception of clinical trials that are contracted through the UPMC Office of Sponsored Programs and Research Support (OSPARS).

Complete the R3 intake form available at <http://rio.pitt.edu/services>. An R3 representative will conduct a review. You will be notified once your R3 review is complete or if anything further is needed.

**\* Describe the protected health information that will be collected from the covered entity and/or the research derived information that will be placed into the medical records:**

Numeric Rating Scale (NRS) with 0- being no pain and 10-being maximum pain will be collected, the amount of total narcotic consumption (measured with morphine equivalent doses of analgesics used to provide pain relief).

Time to patient-controlled analgesia (PCA) initiation on the floor will also be measured and collected from medical record, as well as total PCA hydromorphone consumption over the 48-hour postoperative period.

Post-operative nausea and/or vomiting will be evaluated by nausea score (0-10), frequency of emesis and rescue antiemetic requirement. This information will be collected from the patient's medical record

Adverse events related neuraxial opioids such as pruritus, respiratory depression and urinary retention will be noted. We will also evaluate operative or anesthetic complications, organ morbidity (e.g., pneumonia, renal failure, stroke, cognitive dysfunction, and cardiac failure), bowel complications (prolonged ileus, anastomotic leak, abdominal sepsis) and mortality between the two groups.

Patient demographics and medical history to determine eligibility will also be collected from the medical record.

The patient's medication summary while in the hospital will also be collected from medical record, as well as progress notes from the entire encounter to determine the existence of adverse events.  
information

Information to be placed in the medical record includes response to study treatment including adverse events (side effects). Also a copy of the signed informed consent will be placed in the medical record.





## Electronic Data Management

1. \* Will only anonymous data be collected (select **NO** if identifiers will be recorded at anytime during the conduct of the study)?

Yes  No

Select **all identifiers** to be collected during any phase of the research including screening:

- |                        |                                     |   |                          |
|------------------------|-------------------------------------|---|--------------------------|
| Name:                  | <input checked="" type="checkbox"/> | Internet Protocol (IP) Address:                 | <input type="checkbox"/> |
| E-mail address:        | <input type="checkbox"/>            | Web Universal Resource Locators (URLs):         | <input type="checkbox"/> |
| Social security #:     | <input type="checkbox"/>            | Social security # (for Vincent payment only):   | <input type="checkbox"/> |
| Phone/Fax #:           | <input checked="" type="checkbox"/> | Full face photo images or comparable images:    | <input type="checkbox"/> |
| Account #:             | <input checked="" type="checkbox"/> | Health plan beneficiary #:                      | <input type="checkbox"/> |
| Medical record #:      | <input checked="" type="checkbox"/> | Device identifiers/serial numbers:              | <input type="checkbox"/> |
| Certificate/license #: | <input type="checkbox"/>            | Vehicle identifiers/serial #/license plate #:   | <input type="checkbox"/> |
|                        |                                     | Biometric identifiers, finger and voice prints: | <input type="checkbox"/> |

- a: Will you be collecting any of the following **location data**:  Yes  No  
 \* geographic subdivisions smaller than a State such as street address, city, county, precinct, zip, geocodes, etc.?

- b: Will you be collecting any **date information** such as birth date, death, admission, discharge, date of surgery/service?  Yes  No

c: List any other unique identifying numbers, characteristics or codes related to an individual that are to be collected:

- For ALL identifiable data collected,  Yes  No  
 \* will you be coding the data by removing the identifiers and assigning a unique study ID/code to protect the identity of the participant?

- \* Will the data be **HIPAA de-identified**?  Yes  No

- \* Briefly describe your plan to store identifiable data will be kept in a single coded data separately from the identifiable data: encrypted file on the shared (z:) drive behind the UPMC firewall. All other study-related data (such as paper records and data for analysis) will have all identifiers removed. To protect against the possibility of breach of

confidentiality, all data collected will be identifiable only by a unique subject ID number, and no personal identifiers will be stored with the data. Linkage files identifying subjects will be stored only in the UPMC server and will be linked to the physical record with a subject code. Physical records will be kept in locked files accessible only by study staff; electronic data will be handled and protected as described above on the UPMC server.

2. \* Will sensitive data be collected (e.g., protected health information, mental health, medications, drug/alcohol use, illegal behaviors)?

Yes  No

3. \* Select all locations where data will be stored or accessed (including e.g., personal / employer laptop or desktop):

	Storage Device	Description	Identifiable Data	Sensitive Data	De-Identified/Anonymous Data
<a href="#">View</a>	Server: UPMC Managed Server		yes	yes	yes
<a href="#">View</a>	UPMC owned desktop, laptop or other device		no	no	no

4. \* Select all technologies being used to collect data or interact with subjects:

N/A

## Data Safety and Monitoring

- 1. \* Describe your plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe. The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor:**

The following data and safety monitoring plan will be instituted to ensure the safety of the subjects and to maintain the confidentiality of the research data. The principal investigator, co-investigators and study coordinators will perform a monthly review of the accrued data and incidence of adverse effects to ensure validity and integrity of the data and to reassess the benefit-to-risk ratio on a frequent and regular basis. Subject privacy and research data confidentiality will be ensured by reviewing the adequacy of the secure location of where the data is stored and by making sure it is all de-identified with the coded case numbers as described previously. Since the study investigators, while blinded, will be directly involved with the care of the subjects, they will immediately inform the rest of the investigators if adverse effects occur. Adverse events, data quality and timeliness of participant recruitment will all be reviewed with the team of investigators, who will determine whether the study should be continued as planned, changed or terminated.

- 2. \* Describe your plan for sharing data and/or specimens:**

No data sharing is planned

- 3. If any research data is collected, stored, or shared in a paper format, address what precautions will be used to maintain the confidentiality of the data:**

Paper-based records will be kept in a secure location, computer-based files will be available to personnel involved in the study through access privilege, whenever possible identifiers will be removed from study-related information, patients' computer medical information will only be available through password access.

## Risk and Benefits

1. \* Enter all reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to subjects' participation in the research:

View

Research Activity	Opioid administration
Common Risks	nausea and vomiting
Infrequent Risks	apnea and respiratory depression, skeletal muscle rigidity
Other Risks	No Value Entered

View

Research Activity	Medical Record Review
Common Risks	No Value Entered
Infrequent Risks	Breach of confidentiality
Other Risks	No Value Entered

View

Research Activity	IV Acetaminophen Administration
Common Risks	nausea, vomiting, headache, and insomnia
Infrequent Risks	liver transplant and death
Other Risks	Most of the cases of liver injury are associated with vomiting, constipation, pruritus, agitation

2. \* Describe the steps that will be taken to prevent or to minimize risks:

Investigators who will access the identifiable medical records already have normal clinical access to all necessary records, as granted by the privacy office for job-related needs. Thus, only HIPAA trained research staff will be handling this information and this information will be stored in a locked database protected by the UPMC firewall. Additionally, all data generated under this protocol will be monitored and maintained by the principal investigator. Any databases that contain identifiable information will be stored on a departmental drive on the UPMC network created for the principal investigator, and all data will be deidentified according to the HIPPA "safe harbor" guidelines prior to statistical analysis.

Symptoms of nausea, headache, insomnia will be monitored by the nursing staff on a

regular basis as ordered by the protocol. The anesthesiologists and members of the study team will be available to address any complaints and problems that the study participant may experience 24hours/day 7 days/week. Headaches, insomnia, nausea and vomiting will be treated by protocolized standard management.

The study team will make sure that the maximum recommended dose of Acetaminophen per day will not be exceeded by close monitoring of patient electronic record to avoid liver injury. Patients with high liver enzymes or other liver problems will not be included in the study.

**3. Financial risks - will the subject or insurer be charged for any research required procedures?**

Yes  No

**4. Describe the steps that will be taken to protect subjects' privacy:**

Research intervention will be conducted in a private room with the patient, collected information will be limited to that which is necessary for the goals of the research study, access to the patient's private information will be limited to those involved in the patient's medical care, the initial acetaminophen/placebo infusion will be performed in the surgery room with only the patient, surgeon, surgical staff and physicians who are needed for the performance of the surgery. The following infusions as well as follow up with the patient will be completed one on one with either the investigational staff or a clinician in the patients room.

**5. What steps will be taken in the event that a clinically significant, unexpected disease or condition is identified during the conduct of the study:**

The patient's primary medical team will be immediately notified of the unexpected, clinically significant condition. The patient's clinically significant medical condition will be managed accordingly. If any of the clinically significant medical condition is related to the study, then the patient's participation in the study will be re-evaluated, with the possibility of the patient being withdrawn from the study if this leads to the resolution of the clinically significant medical condition

**6. Describe the potential benefit that individual subjects may experience from taking part in the research or indicate if there is no direct benefit. Do not include benefits to society or others:**

The systematic use of a non-opioid pain adjuvant in colorectal, pancreatic, and major abdominal surgeries as part of a multimodal enhanced recovered after surgery protocol will have a significant impact in improving postoperative pain scores and

reducing overall opioid consumption in the postoperative period. Furthermore, overall patient satisfaction and safety in the perioperative period stand to gain from limiting opioid-related side effects. Successful implementation of non-opioid analgesia in the perioperative period may prevent prolonged hospital stays and decreased patient satisfaction as a result of opioid-related side effects such as nausea/vomiting, prolonged postoperative ileus, cognitive dysfunction, and a multitude of other systemic insults. In doing so, hospital systems will further improve the overall patient care experience while also reducing direct and indirect costs related to prolonged hospital stays and medical management of postoperative complications.

**7. Do you anticipate any circumstances under which subjects might be withdrawn from the research without their consent?**

Yes  No

**\* Describe the circumstances and any procedures for orderly termination:**

- Severe Adverse reactions to any medications given for the study (anaphylaxis, intractable nausea, severe respiratory depression).
- Change in surgical plan that would exclude patient from trial
- Critical medical events during surgery that warrant removal from the trial
- Protocol violations
- Medication errors
- If at any time the patient decides that they do not want to be a participant in the study, then their participation in the study would be discontinued.

**8. Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection and data already collected:**

After withdrawing from the study, each subject's data will be kept for the required data retention period in a secure, locked facility, and will be destroyed after that period. Patients' data might be used for data analysis if deemed necessary/useful (e.g. reason of withdrawal).

## Placebo Arm

- 1. \* Is there a commonly used diagnostic/treatment approach that is currently recognized as being effective for the proposed subjects' disease or condition, and that will be withheld from subjects assigned to the placebo arm of this research study:**

No - subjects assigned to the placebo and experimental arms of the research study will continue to undergo a commonly used diagnostic/treatment approach

- 2. Describe the commonly used diagnostic/treatment approaches that will be withheld from subjects assigned to the placebo arm of this research study:**

Subjects assigned to the placebo arm of the study are still eligible to receive all of the commonly-prescribed pain medications to treat this type of procedure

- 3. Is enrollment into this study limited to individuals in whom the commonly used diagnostic/treatment approaches are known to be ineffective or intolerable?**

no

- 4. Provide a scientific justification for the placebo-control arm of this research study:**

Review of literature on the effect of adding acetaminophen to patients undergoing major abdominal surgical procedures revealed few clinical trials, however the ones that are available include a placebo arm. Further, The placebo-control arm will allow for the clinicians to remain blinded to the treatment allocation of participants which will greatly improve the value of the study

- 5. How long will subjects participate in the placebo arm? Justify why this duration is necessary:**

48 hours

- 6. How frequently will the subject's condition or disease be monitored and compare that to the frequency of monitoring associated with standard care for this disease/condition?**

Participants in both groups will be monitored by the research team while in the hospital for incidence of adverse events, so they will be monitored more frequently than the standard of care.

**7. What specific endpoints will result in discontinuing a subject's participation due to worsening of the subject's disease or condition?**

The same stopping criteria for the intervention arm will be applied to the placebo arm, because clinicians will be blinded to treatment allocation

**8. What is the risk to subjects who receive no active treatment for their disease or condition while in the placebo arm?**

Subjects in the placebo arm will still have their post-operative pain managed as per standard of care for this population at Presbyterian/Montefiore Hospitals.

**9. Describe the planned involvement of a 'contact person' who interacts with the subject on a regular basis and who will notify the investigators immediately of any problems related to the subject's disease or condition:**

Symptoms of nausea, headache, insomnia will be monitored by the nursing staff on a regular basis as ordered by the protocol. The anesthesiologists and members of the study team will be available to address any complaints and problems that the study participant may experience 24hours/day 7 days/week. Headaches, insomnia, nausea and vomiting will be treated by protocolized standard management

*Note: The involvement of the contact person must also be addressed in the consent form*



## Conflict of Interest

### 1. \* Is this an FDA Covered Clinical Study?

Yes  No

Answer **YES** if it is:

- A study of a drug or device in humans to be submitted in a marketing application or reclassification petition that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product); or
- A study in which a single investigator makes a significant contribution to the demonstration of safety.

Do **NOT** include:

- phase I tolerance studies or pharmacokinetic studies;
- clinical pharmacology studies (unless they are critical to an efficacy determination);
- large open safety studies conducted at multiple sites;
- treatment protocols; or
- parallel track protocols.

### 2. \* Does this study involve a Non-Significant Risk Device and you anticipate including the results as part of any type of submission to the FDA for approval of this device?

Yes  No

### 3. \* Is this study funded in part or whole by a PHS Agency?

Yes  No

### 4. \* Does any investigator involved in this study (select all that apply):

- A. Have a financial interest (aggregated value of equity and remuneration during the past or next twelve months) in a publicly-traded entity that either sponsors this research or owns the technology being evaluated or developed that exceeds a 5% ownership interest or a current value of \$10,000?
- B. Receive remuneration (during the past or next twelve months) from a non-publicly traded entity that either sponsors this research or owns the technology being evaluated or developed that exceeds \$10,000?
- C. Have equity in a non-publicly traded entity that either sponsors this research or owns the technology being evaluated or developed?
- D. Have rights as either the author or inventor of intellectual property being evaluated or developed in this research and for which you are receiving royalties, milestone fees, or other proceeds that have or will exceed \$10,000 in any 12-month period (include payments through the University of Pittsburgh, the Veterans Administration Pittsburgh Healthcare System, UPMC, and University of Pittsburgh Physicians)?
- E. Have an officer or management position with a company that either sponsors this research or owns the technology being evaluated or developed?
- F. Receive compensation of any amount when the value of the compensation would be affected by the outcome of this research, such as compensation that is explicitly greater for a favorable outcome than for an unfavorable outcome or compensation in the form of an equity interest in the entity that either sponsors this research or owns the technology being evaluated or developed?
- None of the above options apply and there are no other financial conflicts of interest in the conduct of this research.

**5. Provide the name of the investigator(s) and describe the nature of the Significant Financial Interest(s):**

## Ancillary Reviews

**1. Ancillary reviews or notifications selected below are required based on previous answers to questions. If a selection is incorrect, return to the appropriate page and adjust the answers to questions on that page:**

- Conflict of Interest (**COI**)
- Clinical and Translational Research Center (**CTRC**)
- Data Security
- Honest Broker
- UPMC Investigational Drug Service
- Pitt Medical School Review
- Office of Investigator-Sponsored IND & IDE Support (**O3IS**)
- RCCO Business **Manager** (required for industry sponsored studies)
- Religious Directives
- Scientific Review
- Health Record Research Request (**R3**) (required if using UPMC clinical data and authorization for other UPMC data sources for research)
- UPMC Office of Sponsored Programs and Research **Support** (using UPMC facilities and/or UPMC patients during the conduct of the study)

**2. Additional ancillary reviews the PI may choose to include as needed for the research:**

- Human Stem Cell Oversight (**hSCRO**)
- Institutional Biosafety Committee (**IBC**)(study involves deliberate transfer of recombinant or synthetic nucleic acid molecules)
- Radioactive Drug Research Committee (**RDRC**)(study involves the evaluation or use of procedures that emit ionizing radiation)

## Good Clinical Practice (GCP) Training

1. \* Regardless of funding source, is this study a clinical trial (as defined by the NIH)?
- Yes  No

## ClinicalTrials.gov Information

Visit the University of Pittsburgh Office for [ClinicalTrials.gov website](#) or contact [ctgov@pitt.edu](mailto:ctgov@pitt.edu) for further information.

2. \* Was this study registered, or will it be registered, on ClinicalTrials.gov?
- Yes  No
3. \* Is the University of Pittsburgh or UPMC the Sponsor Organization for this study record?
- Yes  No

\* Who will be the Responsible Party for this study record?

Principal Investigator of this IRB application

## Supporting Documents

1. Attach any additional supporting documents not previously uploaded. Name the documents as you want them to appear in the approval letter:

	Document	Category	Date Modified	Document History
<a href="#">View</a>	<a href="#">DSMB 4(0.01)</a>	Other	4/17/2019	<a href="#">History</a>
<a href="#">View</a>	<a href="#">DSMB 3(0.01)</a>	Other	4/17/2019	<a href="#">History</a>
<a href="#">View</a>	<a href="#">DSMB 2(0.01)</a>	Other	4/17/2019	<a href="#">History</a>
<a href="#">View</a>	<a href="#">DSMB 1(0.01)</a>	Other	4/17/2019	<a href="#">History</a>

## Add Drug Information

### 1. Select the drug:

Acetaminophen

If you cannot find the drug in the list above, enter its information here:

**Generic name:**

**Brand name:**

### 2. \* Purpose of their use:

FDA approved for use in management of mild-to-moderate pain, moderate-to-severe pain with adjunctive opioid analgesics, and reduction of fever in patients 2 years and older.

### 3. \* FDA status:

Meets current FDA approved indication and usage labeling

### 4. Attach files related to this drug:

Document	Category	Date Modified	Document History
<a href="#">View Acetaminophen Injection FDA label.pdf(0.01)</a>	Drug Attachment	4/16/2019	<a href="#">History</a>

Attachments may include a copy of the package insert, investigator brochure, product labeling, or verification of any IND number.

## Add Storage Information

**1. \* Select a Storage Type:**

Server: UPMC Managed Server

**2. Description:**

**3. \* Will identifiable data be stored in this location?**

Yes  No

**4. \* Will sensitive data be stored in this location?**

Yes  No

**5. Will de-Identified or anonymous data be stored in this location?**

Yes  No

**6. Provide additional information as needed:**

## Add Storage Information

**1. \* Select a Storage Type:**

UPMC owned desktop, laptop or other device

**2. Description:**

**3. \* Will identifiable data be stored in this location?**

Yes  No

**4. \* Will sensitive data be stored in this location?**

Yes  No

**5. Will de-identified or anonymous data be stored in this location?**

Yes  No

**6. \* Is anti-virus software installed and up to date on all devices and are the operating systems kept up-to-date on all devices?**

Yes  No

**7. Provide additional information as needed:**



## Risk

### 1. \* Research Activity:

Opioid administration

### 2. Common Risks:

nausea and vomiting

### 3. Infrequent Risks:

apnea and respiratory depression, skeletal muscle rigidity

### 4. Other Risks:

## Risk

**1. \* Research Activity:**

Medical Record Review

**2. Common Risks:**

**3. Infrequent Risks:**

Breach of confidentiality

**4. Other Risks:**

## Risk

### 1. \* Research Activity:

IV Acetaminophen Administration

### 2. Common Risks:

nausea, vomiting, headache, and insomnia

### 3. Infrequent Risks:

liver transplant and death

### 4. Other Risks:

Most of the cases of liver injury are associated with vomiting, constipation, pruritus, agitation

