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Epidurals in Pancreatic Resection Outcomes (E-PRO) study: protocol for a randomized controlled trial

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ABSTRACT

Introduction: Epidural analgesia provides an important synergistic method of pain control. In addition to reducing perioperative opioid consumption, the deliverance of analgesia into the epidural space, effectively creating a sympathetic blockade, has a multitude of additional potential benefits, from decreasing the incidence of postoperative delirium to reducing the development of persistent post-surgical pain (PPSP). Prior studies have also identified a correlation between the use of epidural analgesia and improved oncologic outcomes and survival.

Methods: The Epidurals in Pancreatic Resection Outcomes (E-PRO) study is a prospective, single-center, randomized controlled trial. 150 patients undergoing either pancreaticoduodenectomy or distal pancreatectomy will be randomized to receive an epidural bupivacaine infusion following anesthetic induction followed by continued epidural bupivacaine infusion postoperatively in addition to the institutional standardized pain regimen of hydromorphone patient-controlled analgesia, acetaminophen, and ketorolac (intervention group) or no epidural infusion and only the standardized postoperative pain regimen (control group). The primary outcome was the postoperative consumption of morphine or morphine-equivalents. Secondary outcomes include patient-reported postoperative pain numerical rating scores (NRS), trend and relative ratios of serum inflammatory markers (IL-1b, IL-6, TNF-a, IL-10), occurrence of postoperative delirium, development of PPSP as determined by quantitative sensory testing, and disease free and overall survival.

Ethics and dissemination: The E-PRO trial has been approved by the institutional review board. Recruitment began in May 2016 and will continue until the end of May 2018. Dissemination plans include presentations at scientific conferences and scientific publications.

Registration details: This study is registered at clinicaltrials.gov, NCT02681796 (last updated September 2016).

Trial registration number: NCT02681796 (last updated September 2016).

Strength and limitations of this study:

- prospective randomized control trial
- longitudinal follow-up post-operatively
- limited to single institution

INTRODUCTION

Background and Rationale

Epidural Analgesia

The utilization of regional analgesia as a compliment to traditional pain management techniques has become an increasingly common practice at many institutions. Placed pre-operatively, epidural analgesia provides an important synergistic method of pain control post-operatively. In addition to its usefulness as a pain management adjunct, the deliverance of analgesia into the epidural space, effectively creating a sympathetic blockade, has a multitude of potential additional benefits.

Previous studies have examined the use of epidurals in abdominal surgeries with a small number of retrospective trials focusing on the use of epidurals in pancreatic resections[1]. While these retrospective studies demonstrated an improvement in patient-reported pain scores post-operatively, objective measures are still needed to quantify these improvements in pain control[2]. Prior studies have also highlighted a correlation between poor postoperative pain and the development of persistent post-surgical pain (PPSP)[3,4,5]. As epidural analgesia creates a sympathetic blockade, its intraoperative and postoperative use can mitigate the body's inflammatory response and reduce the activation of peripheral and central nervous systems pathways involved in the development of persistent pain syndromes[6]. Interleukin-1-beta (IL-1b), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-a) are three pro-inflammatory cytokines involved in the transition from acute pain states to chronic pain syndromes[7]. Interleukin-10 (IL-10) is an anti-inflammatory cytokine that helps modulate the body's stress response. IL-1b, IL-6, TNF-a, and IL-10, and the relative balance of the pro- and anti-inflammatory response, have all been implicated in nociceptive pathways and elevated levels have been found in chronic pain processes[8]. While our current understanding of the complex modulation pathways of pain is limited, circulating IL-6 has been demonstrated in the up-regulation of central and peripheral nociceptive receptors, thereby generating the perception of pain, and potentially establishing the link between acute and chronic pain[9,10]. This is of particular importance in our study population of patients with pancreatic diseases for whom adequate pain control is a critical factor in maintaining good quality of life[11,12].

In the immediate postoperative period, the use of epidural analgesia can improve other measures of patient recovery and healing, such as promoting gut motility and reducing the incidence of postoperative delirium. Along with reducing total opioid use, epidural analgesia produces a sympathectomy, allowing for dominance of the parasympathetic system, and further expediting the return of bowel function[13,14,15]. With delayed gastric emptying as one of the most common complications and reasons for readmission after pancreatic resections, this valuable benefit of epidural analgesia requires further investigation[16,17]. Delirium is another common postoperative complication that is associated with poor patient outcomes, including functional decline and death, and an effective prophylactic treatment remains to be identified. Through the effects of decreased intraoperative anesthetic requirement and postoperative opioid use, epidural analgesia may have a potential protective role against postoperative delirium.

The effect of epidural analgesia in suppressing the inflammatory cascade is of particular interest to the field of oncology. In certain types of cancers, including pancreatic, the oncogenic process generates an inflammatory environment that propagates the growth of malignant lesions and continued inflammatory conditions have been implicated in metastatic disease[18,19,20]. Pain

can further exacerbate systemic inflammation[21]. In additional to mitigating post-surgical pain, the sympathectomy resulting from epidural analgesia also reduces the body's overall inflammatory conditions[22,23]. This attenuation of the heightened postoperative inflammatory state of the body may provide an additional means of reducing progression of disease.

Pancreatic Diseases

With improved detection and imaging modalities, the incidence of pancreatic disease, and subsequently, pancreatic operations, has increased[24,25,26]. Pancreatic resection continues to be the primary surgical treatment in the treatment of many benign and malignant pancreatic diseases, with an estimated 4,000 operations performed annually in the United States [27]. However, the mean 5-year survival for malignant pancreatic disease remains the lowest of all cancers at 6%, with 70-85% of patients dying of systemic recurrence, not just local disease[28,29,30]. While the search continues for earlier screening methods, the development of adjunctive therapies to surgical resection remains the most promising target of efforts to improve outcomes in malignant diseases of the pancreas. In particular, in recent years, a paradigm shift has occurred in the study of pancreatic malignancies where pancreatic cancer is viewed as a systemic disease, even in early stages, requiring a systemic approach in additional to regional disease control[31,32,33,34]. In previous studies, primarily in prostate and colorectal malignancies, the use of epidural analgesia has suggested a correlation with improved oncologic outcomes and survival[35,36]. Given the role between inflammation and cancer development and recurrence, and the sympathetic blockade created by epidural analgesia, the significance of epidural analgesia in improving oncologic outcomes warrants continued investigation.

METHODS AND ANALYSIS

Study Design

The Epidurals in Pancreatic Resection Outcomes (E-PRO) study is a prospective, single-center, randomized controlled trial. This study has been approved by the Institutional Review Board at Washington University in St. Louis.150 patients undergoing either pancreaticoduodenectomy or distal pancreatectomy will be randomized to receive an epidural infusion of 0.125% bupivacaine starting at 5 ml/hr (range of 5-8 ml/hr) following anesthetic induction followed by a standard epidural infusion of 0.1% bupivacaine at 4-6 ml/hr postoperatively in addition to the institutional standardized pain regimen of hydromorphone patient-controlled analgesia, IV acetaminophen, and ketorolac (intervention group) or no epidural infusion and only the standardized postoperative pain regimen (control group). Follow-up information will be collected from the medical record for up to 2 years post-operatively. The study design is outlined in Figure 1.

Eligibility Criteria

Patients 18 years old or older, who able to understand and sign an Institutional Review Board (IRB)-approved informed consent form, and who are undergoing either pancreaticoduodenectomy or distal pancreatectomy will be eligible for study inclusion. Patients will be excluded if they fulfill any one of the following criteria: indication for operative intervention being chronic pancreatitis, currently on warfarin with an INR>1.4 or clopidogrel

that cannot be discontinued 7 days prior to surgery, most recent INR prior to surgery >1.4, most recent platelet count prior to surgery <70,000/mcl, chronic opioid use as defined by use of more than 20mg oxycodone, or equivalent, daily, history of pre-existing neuropathic pain conditions, known medical history of significant psychiatric or cognitive impairment, or history of HIV, Hepatitis B, and/or Hepatitis C. Patients will be consented and enrolled during a clinic or preoperative evaluation appointment.

Baseline Assessment

Each study participant will be randomized into the control group with standard of care pain management regiment or the intervention group with the addition of epidural analgesia. Randomization will occur via a randomized number generation by the PI.

Patients will have the standard of care preoperative evaluation at the Barnes Jewish Hospital Center for Preoperative Assessment and Planning. Routine laboratory tests including complete blood count, comprehensive metabolic panel, and coagulation studies will be obtained and reviewed.

In patients receiving chronic antiplatelet or anticoagulant medications, the following procedure will be practiced to minimize the risk of bleeding (per American Society of Regional Anesthesia and Pain Medicine guidelines[37]):

Acetyl Salicylic acid (ASA, aspirin) or other NSAIDS may be continued prior to epidural catheter insertion. Clopidogrel use must be discontinued seven days before the procedure. The study participant's treating physician (e.g. surgeon, cardiologist, neurologist) will be consulted prior to the discontinuation of clopidogrel. Participants receiving warfarin will proceed with the following schedule: if INR < 1.4, subject may proceed with epidural catheter insertion. If INR >1.4, the participant's treating physician will be consulted whether warfarin can be discontinued until INR reaches <1.4, or the subject can be switched to Low Molecular Weight Heparin (LMWH), which can be discontinued 36 hours before catheter insertion. INR/PTT will be assessed on the day of epidural catheter insertion in all patients on anticoagulant (but not antiplatelet) therapy.

Study participants will undergo a complete medical history and physical examination, and the following baseline assessments:

1. Evaluation of hypersensitivity or dynamic mechanical allodynia to brush stimulation in the upper abdomen[38].
2. Quantitative sensory testing (QST) to assess warm and cold detection thresholds, heat and cold pain thresholds, mechanical detection and pain thresholds, presence of wind-up (enhanced temporal summation) to pinprick (Supplemental 1).
3. Screening for psychological risk factors for acute and chronic pain using Hospital Anxiety and Depression Scale (HADS)[39].
4. Baseline assessment for delirium using the 3D-CAM instrument.
5. Baseline assessment of serum inflammatory markers (IL-1b, IL-6, TNF-a, IL-10).

Interventions

Post-operatively, all patients will receive a standardized pain regimen including a hydromorphone PCA (initial settings of no bolus dose, 0.25 mg per demand dose, minimal interval dose time of 10 minutes), acetaminophen (1000 mg every 6 hours for 24 hours), and

ketorolac (15 mg every 6 hours for 72 hours) per surgeon's preference. Study group patients will have an epidural bupivacaine infusion beginning in the operating room.

An epidural infusion of 0.125% bupivacaine starting at 5 ml/hr (range of 5-8 ml/hr) will be started after induction of anesthesia. Epidural narcotic consisting of fentanyl 50 mcg will be administered with sterile precaution by the anesthesia provider before starting the epidural infusion. Epidural boluses of 0.125% bupivacaine may be administered as guided clinically. A phenylephrine infusion can be used to maintain adequate blood pressure maintaining mean arterial pressures (MAP) above 60 mmHg. The epidural infusion can be paused if vasopressor requirements exceed 1 mcg/kg/min of phenylephrine or 0.1 mcg/kg/min of norepinephrine. The epidural infusion is to be paused if hemodynamics become unstable, either due to excessive blood loss or MAP consistently below 60 mmHg. The epidural infusion can be resumed when hemodynamics are stable.

The bupivacaine 0.125% epidural infusion is to be discontinued in the OR at the end of surgery and a standard epidural infusion of 0.1% bupivacaine at 4-6 ml/hr will be started in the PACU. The epidural infusion is followed up by an Acute Pain Service in the postoperative period that will titrate the infusion based on the patients' self-reported pain scores and MAP values.

Outcomes

Primary Outcomes

The primary study outcome is the consumption of morphine or morphine-equivalent in patients undergoing pancreatic resections in the control group compared with the study group. Each subject's morphine or morphine-equivalent consumption will be assessed every 24 hours. All subjects will be assessed daily during their postoperative inpatient admission by a trained member of the Acute Pain Service who is blinded to the treatment arm of the study.

Secondary Outcomes

Study team members blinded to the treatment group of the patient will assess all secondary outcomes. Various measures of patient recovery and healing in the initial postoperative period will be evaluated, including visual analog scores (VAS), intravenous fluid requirements, anti-emetic doses, and return of bowel function. Serum inflammatory markers will be evaluated serially, preoperatively on day of surgery, three hours after the start of surgical incision in the operating room, on postoperative day 2, and at the initial postoperative visit 2-6 weeks after surgery. Postoperative delirium assessments will be performed when patients can be aroused sufficiently in order to be assessed for delirium (Richmond Agitation-Sedation Scale (RASS) > -4). Each patient will be assessed for delirium on postoperative day 2 as postoperative delirium typically first manifests 24-96 hours after surgery. For non-verbal patients the CAM-ICU instrument will be used and for verbal patients, the 3D-CAM instrument will be used[40]. As delirium is a fluctuating disorder and can be missed with sporadic delirium assessments, a structured method of chart review will be used to complement the clinical assessments. This combined approach (3D-CAM interview or CAM-ICU plus chart review) increases the sensitivity and retains specificity in detecting incident delirium. The trial staff has undergone formal training in clinical delirium assessment and on the chart review methodology.

Patients will be seen for their initial postoperative weeks at 2-6 weeks after hospital discharge and will undergo repeat PPSP evaluation at that time.

Patients will continue to be followed in clinic for 2 years postoperatively with laboratory and radiologic evaluation as deemed appropriate by the primary surgeon. Patients will be followed for tumor recurrence and overall survival. Data will be collected directly from subject's medical record; no study-specific procedures will be implemented at follow up visits.

Sample Size

For purposes of sample size estimation, total morphine consumption in the first 72 hours after surgery is the primary outcome of the study. Based on our prior experience, sample size estimation will be based on the following assumptions[41]: Expected morphine consumption is 30 milligrams intraoperatively, 30 mg on postoperative day 1 (POD1), 20 mg on POD2 and 10 mg on POD3. Therefore, expected total morphine consumption in the first 72 hours is, on average, 80 mg. Then, assuming that the standard deviation of morphine consumption is 30 mg, that a 20 mg difference in morphine consumption between groups is a clinically meaningful reduction of opioid use and assuming normal distribution of morphine consumption in both patient groups, the proposed sample size for a = 0.05 and b = 0.2 would be 37 patients per group (74 patients in total). However, we propose to increase the sample size of the study to 150 total patients to account for patients lost to follow-up, inability to complete the scheduled pancreatic resection, data errors, and other un-anticipated study problems.

Recruitment

Participants will be recruited primarily through the Washington University Hepatobiliary-Pancreatic Surgery clinics. Subjects will be given verbal (initially) and then written descriptions of the study aims, procedures, risks, and benefits, and will be required to give written informed consent. A member of the investigative team provides all study descriptions, informed consent, and answers all questions. No deception is required for the purposes of this study. All subjects will be aware of the randomization used in this study to either the control or intervention group. Subjects are informed verbally and in writing that participation is voluntary and they may refuse to participate and may withdraw from the study at any time without penalty.

Allocation

Participants will be randomized in a 1:1 ratio into the control group with standard of care pain management regimen or the intervention group with the addition of epidural analgesia. Randomization will occur via randomized number generation.

This is a single-blind study. Patients and the primary investigative team will be aware of the randomization. However, all study members performing data collection will be blinded to the randomization.

Data Analysis and Management

Data analysis for this study will focus on the comparison of patient outcomes (postoperative morphine/morphine-equivalent consumption, measures of postoperative recovery, inflammatory markers, 3D-CAM/CAM-ICU assessments, QST) between the intervention and control study groups. Based on data distribution, continuous variables will be compared between

the two groups using student's t test or the Mann Whitney U test as appropriate. When appropriate, significance of findings will be adjusted for multiple comparisons using the Bonferroni correction method.

The Center for Biomedical Informatics at Washington University will be used as the central location for data collection and management. Since 2008, Washington University has hosted Research Electronic Data Capture (REDCap), a secure, web-based application for building and storing online research and clinical trial databases. The REDCap servers are securely housed in an on-site limited access data center managed by the Center for Biomedical Informatics at Washington University. All web-based information transmission is encrypted and all data are stored on a private firewall protected network. All users are assigned individual user IDs and passwords and individual access is restricted on a role-specific basis. REDCap was developed specifically around HIPAA guidelines and is also implemented and maintained in accordance with institutional security guidelines.

Monitoring

The study team will monitor all study participants for adverse events. The principal investigator will report all unanticipated problems or adverse events, all conditions of noncompliance, and any new information that may affect the continued or current enrollment of study participants to the IRB. All events will be reported to the IRB within 10 working days of the event or of notification of the principal investigator of the event. The death of a study participant must be reported to the IRB within 1 working day of the event or of notification of the principal investigator of the event.

The specific monitoring plan for this investigation is commensurate with the risks and the size and complexity of the investigations planned. The potential risks are attributable to performing insertion of the epidural catheter and the use of bupivacaine for neuraxial analgesia. Based on these considerations, the monitoring plan involves engaging a colleague from the Department of Anesthesiology not involved in the study to serve in a monitoring capacity. Based on the small size and relatively low risks nature of the protocol, only a third person (the colleague), rather than a full Data Safety Monitoring Board will be used. The colleague will be an anesthesiologist knowledgeable in the risks associated with nerve blocks and local anesthetic administration. This individual will review the annual summary of adverse events. In addition, this colleague will review all reports of a Serious Adverse Event, or an Unexpected Adverse Event.

ETHICS AND DISSEMINATION

Ethics Approval and Consent

The E-PRO trial was approved by the Washington University IRB. Study recruitment and enrollment began in May 2016 and will continue through the end of 2017. Potential study participants will be given verbal and then written descriptions of the study aims, procedures, risks, and benefits, and written informed consent will be obtained for all participants. All participants are informed verbally and in writing that participation is voluntary and they may refuse to participate and may withdraw from the study at any time without penalty.

Confidentiality

Only the investigators and research team will have access to any protected health information of study participants and any study data. All subjects will be assigned a study ID number. All study data and samples will be coded with the assigned study ID number. A key to the code linking code numbers to patient names will be kept at a separate location, under lock and key; this link will be destroyed at the conclusion of this study. All data will be recorded by a member of the research team and will be stored in a password-protected electronic database stored on the departmental network drive. Study data will be not be entered into participants' medical records.

Dissemination

Dissemination plans include presentations at scientific conferences and scientific publications.

CONCLUSIONS

This trial investigates a wide spectrum of potential benefits to patients undergoing pancreatic resection. During the initial postoperative period, the use of epidural analgesia can aid in improving postoperative pain control, decreasing opioid consumption, reducing the incidence of delirium, and expediting recovery. In addition to improving immediate post-surgical pain control, epidural analgesia may reduce the development of persistent post-surgical pain, which can persist for weeks to years after surgery. Lastly, epidural analgesia can help reduce the body's stress response to a major operation, which has been linked to malignant progression and spread. Based on this trial, we seek to establish the role of epidural analgesia as part of the standard of care in future patients undergoing pancreatic operations.

Authors' Contributions

LMP and MMB are the primary authors of the E-PRO protocol. Their contributions include conceptualizing the study design, drafting and editing the protocol, and creating the electronic database REDCap used for data collection. WGH contributed to the E-PRO protocol by editing the protocol and recruiting patients for enrollment. SH contributed to the E-PRO protocol by conceptualizing the study design, drafting and editing the protocol, and supervising data collection. LW contributed to the E-PRO protocol by editing the protocol, recruiting patients, and collecting data. MK contributed to the E-PRO protocol by recruiting patients and collecting data. KF contributed to the E-PRO protocol and editing the protocol, creating the electronic database REDCap, coordinating patient enrollment and data collection. RAS contributed to the E-PRO protocol by conceptualizing the study design and editing the protocol. All authors including LMP, WGH, SH, LW, MK, KF, RAS, and MMB have critically revised the E-PRO protocol and approved the final version. All authors agree to be accountable for the accuracy and integrity of all aspects of the E-PRO trial.

Funding Statement

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Competing Interests Statement
None

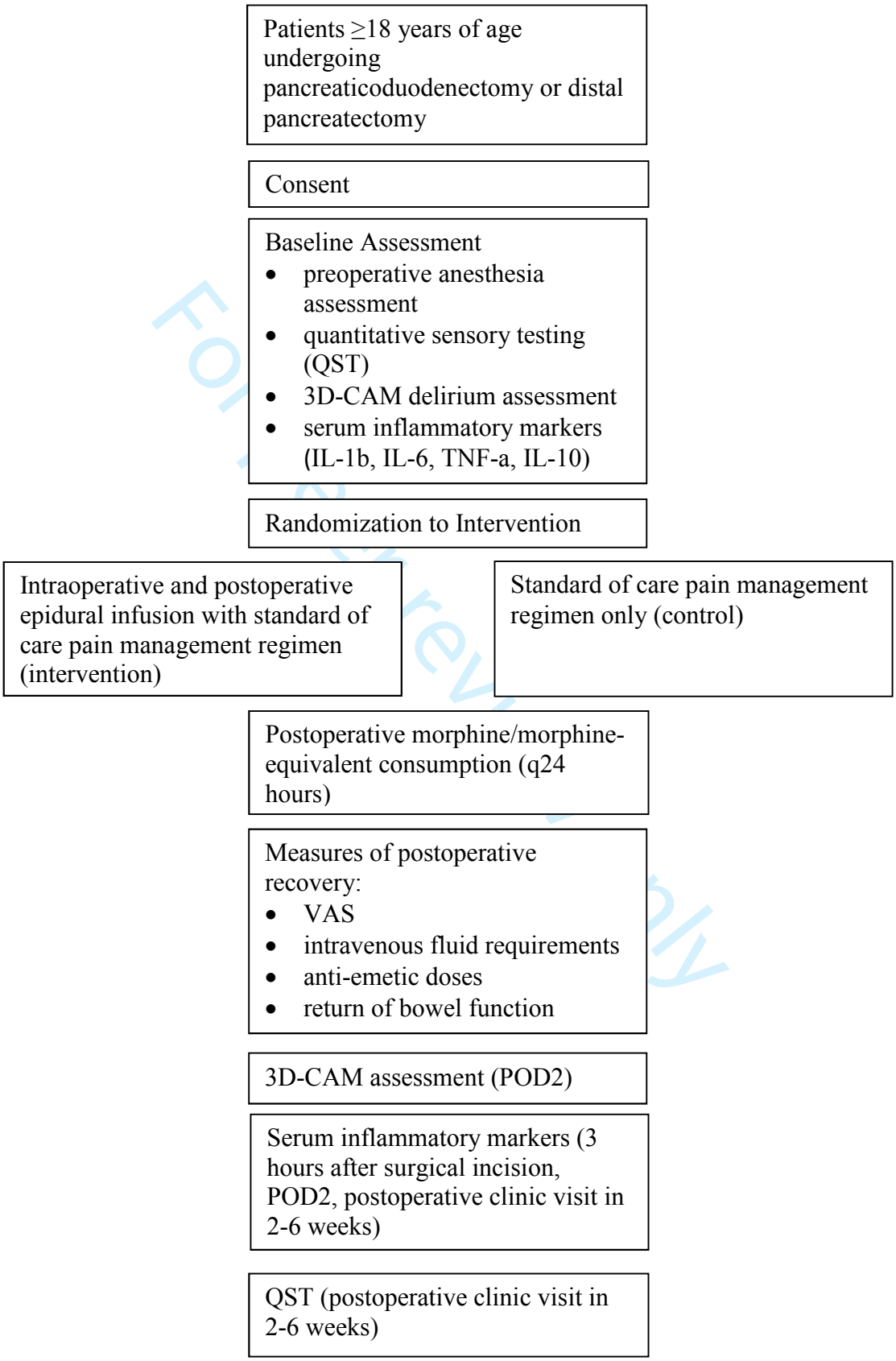
FIGURE LEGEND

Figure 1. Study design.

SUPPLEMENTAL FILES

Supplemental 1. Quantitative sensory testing (QST) protocol.

Figure 1. Study design.



Supplemental 1. Quantitative sensory testing (QST) protocol.

Quantitative sensory testing will be performed in the main assessment area on the abdomen, in close proximity to the surgical incision.

A description of the QST procedures follows:

Thermal detection and thermal pain thresholds
Equipment: The Thermal Sensory Analyzer (TSA-II or PATHWAY platform - Medoc, Ramat Yishai, Israel) will be used to determine thermal detection and pain thresholds. This equipment is used globally for functional assessment of pain and temperature-conducting nerve fibers (C and A-delta fibers).
Method and Background: Using the thermal sensory analyzer, cold and warm detection thresholds (CDT and WDT, respectively), as well as cold and heat pain thresholds (CPT and HPT, respectively) will be determined[42,43]. The thermode with contact area of 9.0 cm^2 is applied to the tested site, and all thresholds are determined by continuous ramping of temperature from 32°C baseline temperature by 1°C/s until the subject presses the 'stop' button. Cut-off temperatures are 0°C and 50°C, to minimize thermal damage to the skin. The baseline temperature to which the thermode returns before each test is 32°C. The average threshold is calculated from three measurements in each area.

Determination of mechanical detection threshold (MDT)
Equipment: A set of standardised von Frey filaments (#1.65, #2.35, #2.44, #2.83, #3.22, #3.61, #3.84, #4.08, #4.17, #4.31, #4.74, #4.93, #5.07, #5.18, #5.46, #5.88, #6.10, #6.45, 6.65. The contact area of the filaments with the skin is of uniform size (<1 mm^2) and texture.

Methods and Background: Standardised von Frey filaments[44,45] will be used in a modified "method of limits" manner using 3 series of increasing and decreasing stimulus intensities to determine the geometric average as the tactile detection threshold of the affected and unaffected skin areas[46].

Von Frey filaments of different stimulus intensities are used to determine the tactile detection thresholds. A #5.07 filament (eliciting 10 gram force)* is applied first, followed by filaments of consecutively lower intensity until the patient cannot detect the stimulus being applied. This respective force represents the first threshold value. The order in which the stimuli are applied is then reversed and stimuli of consecutively greater intensity are applied until sensation is detected (this intensity becomes the second value). Again filaments with decreasing intensity are applied until in total 3 upper and lower values of detection are fulfilled from which the mechanical detection threshold can be determined.

* In case the first von Frey filament (#5.07) is not detected, the next highest intensity filament which can be detected must be used as a starting intensity. However, the relevant force of this stimulus is not documented. Filaments with consecutively lower intensity are applied until the patient cannot detect the stimulus being applied. The procedure is followed as above; until in total 3 upper and lower values of detection are fulfilled from which the mechanical detection threshold can be determined.

Determination of mechanical pain thresholds (MPT)
Equipment: Same as for MDT determination.
Methods and Background:
Standardised von Frey filaments will be used in a modified "method of limits" manner using 3 series of increasing stimulus intensities to determine the average mechanical pain threshold of the affected and unaffected skin areas.
Beginning with an applied force of 8mN, stimuli increase in intensity until the sensation induced by increased pressure can be described as 'painful'. The corresponding force is used to represent the first MPT value. The procedure is then repeated a total of 3 times and until a total of 3 values are obtained, from which the mean mechanical pain threshold can be determined.

Determination of wind-up ratio (WUR)
Equipment: A pinprick stimulus with standardised intensity (#6.10 von Frey filament, approx. 98 gram) and a flat contact area of 0.25mm diameter.
Methods and Background: In this test a pinprick) is first applied singularly. After that a series of 10 identical pinprick stimuli are applied with a frequency of 1 s^{-1} within an area of 1 cm^2. Immediately following the single stimulus and series of stimuli, an evaluation of the sensation must be provided according to NRS (0-10, '0': 'no pain', '10': 'worst pain imaginable'). A ratio is calculated using these values. This procedure shall be repeated twice. A geometric average of the 'wind-up' is calculated from the two ratios[47,48].

3D-CAM Instrument

For Research : Version 3.0

Evaluator:

Date:

Patient:

Time:

COGNITIVE FUNCTION

Now I'd like to ask you some questions to check your memory. Don't worry if you don't know the answers.

[YOU MAY REPEAT EACH QUESTION ONCE]

(WRITE PATIENT'S ANSWERS TO ALL QUESTIONS AND CIRCLE NUMBER AS INDICATED)

ORIENTATION	CORRECT	ERROR	REF	DK/No Response
1. **What is the year**? _____	1	2	7	8
2. **What is the day of the week**? _____	1	2	7	8
3. **What type of place is this?** _____	1	2	7	8

***If any of 3 items above are anything other than correct, feature 3 is present**

DIGIT SPAN

[SAY DIGITS AT RATE OF ONE PER SECOND]

Now I am going to read some numbers, but I want you to repeat them in backwards order from the way I read them to you. So for example if I said 6-4, you would say 4-6.

DIGITS BACKWARD	Response	Correct	Error	REF	DK/No Response
4. **7 - 5- 1**	___ - ___ - ___	1	2	7	8
5. **8 - 2 - 4 - 3**	___ - ___ - ___ - ___	1	2	7	8

6. DAYS OF WEEK BACKWARDS

Can you tell me the days of the week backwards? Say Saturday as your first day.

(May prompt with: "what is the day before Saturday? or if subject stops with Day X, say " what is the day before day X? …." This prompt may be used 2 times in total. If participant starts reciting days forward repeat overall instructions.

Day	Response	Correct	Error	REF	DK/No Response
Saturday	_____	1	2	7	8
Friday	_____	1	2	7	8
Thursday	_____	1	2	7	8
Wednesday	_____	1	2	7	8
Tuesday	_____	1	2	7	8
Monday	_____	1	2	7	8
Sunday	_____	1	2	7	8

Record response verbatim

Coding Instructions: If the subject leaves 1 day out, total recorded = 6, if 2 days are reversed, total recorded =5

7. MONTHS OF YEAR BACKWARDS

Can you tell me the months of the year backwards? Say December as your first month?

(*May prompt with: "what is the month before December? or if the subject stops with Month X, " say what is the month before Month X? …." This prompt may be used 2 times in total. If participant starts reciting months forward repeat overall instructions)*

Month	Response	Correct	Error	REF	DK/No Response
December	_____	1	2	7	8
November	_____	1	2	7	8
October	_____	1	2	7	8
September	_____	1	2	7	8
August	_____	1	2	7	8
July	_____	1	2	7	8
June	_____	1	2	7	8
May	_____	1	2	7	8
April	_____	1	2	7	8
March	_____	1	2	7	8
February	_____	1	2	7	8
January	_____	1	2	7	8

Record response verbatim.

Coding Instructions: If the subject leaves one month out, total recorded = 11, if the months are reversed, total recorded = 10

*****If any of items 4, 5, 6, or 7 above are anything other than correct, feature 2 is present***

References

[1] Park WY, Thompson JS, Lee KK. Effect of epidural anesthesia and analgesia on perioperative outcome: a randomized, controlled Veterans Affairs cooperative study. *Ann Surg*. 2001;234:560-571.

[2] Choi DX, Schoeniger LO. For patients undergoing pancreatoduodenectomy, epidural anesthesia and analgesia improves pain but increases rates of intensive care unit admission and alterations in analgesics. *Pancreas*. 2010;39(4):492-7.

[3] Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet*. 2006;367(9522):1618-25.

[4] Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. *Expert Rev Neurother*. 2009;9(5):723-44.

[5] Pogatzki-Zahn EM, Schnabel A, Zahn PK. Room for improvement: unmet needs in postoperative pain management. *Expert Rev Neurother*. 2012;12(5):587-600.

[6] Zhang JM, An J. Cytokines, inflammation, and pain. *Int Anesthesiol Clin*. 2007;45(2):27-37.

[7] DeVon HA, Piano MR, Rosenfeld AG, Hoppensteadt DA. The association of pain with protein inflammatory biomarkers: a review of the literature. *Nurs Res*. 2014;63(1):61-62.

[8] Uceyler N, Eberle T, Rolke R, Birklein F, Sommer C. Differential expression patterns of cytokines in complex regional pain syndrome. *Pain*. 2007;132(1-2):195-205.

[9] De Jongh RF, Vissers KC, Meert TF, Booij LH, De Deyne CS, Heylen RJ. The role of interleukin-6 in nociception and pain. *Anesth Analg*. 2003;96(4):1096-103.

[10] Woolf CJ, Costigan M. Transcriptional and posttranslational plasticity and the generation of inflammatory pain. *Proc Natl Acad Sci U S A*. 1999;96(4):7723-30.

[11] Burger V, D'Olimpio JT. Improving quality of life through pain control. *Clin J Oncol Nurs*. 2013;17(2):117-8.

[12] Chan C, Franssen B, Dominguez I, Ramirez-Del Val A, Uscanga LF, Compuzano M. Impact on quality of life after pancreatoduodenectomy: a prospective study comparing preoperative and postoperative scores. *J Gastrointest Surg*. 2012;16(7):1341-6.

[13] Carroll J, Alavi K. Pathogenesis and management of postoperative ileus. *Clin Colon Rectal Surg*. 2009;22(1):47-50.

[14] Leslie JB, Viscusi ER, Pergolizzi JV Jr, Panchal SJ. Anesthetic routines: the anesthesiologist's role in GI recovery and postoperative ileus. *Adv Prev Med*. 2011;2011: 976904. Epub 2010 Dec 29.

[15] Person B, Wexner SD. The management of postoperative ileus. *Curr Probl Surg*. 2006;43(1):6-65.

[16] Emick DM, Riall TS, Cameron JL, Winter JM, Lillemoe KD, Coleman J, Sauter PK, Yeo CJ. Hospital readmission after pancreaticoduodenectomy. *J Gastrointest Surg*. 2006;10(9):1243-52.

[17] Ahmad SA, Edwards MJ, Sutton JM, Grewal SS, Hansenman DJ, Maithel SK, Patel SH, Bentram DJ, Weber SM, Cho CS, Winslow ER, Scoggins CR, Martin RC, Kim HJ, Baker JJ, Merchant NB, Parikh AA, Kooby DA. Factors influencing readmission after pancreaticoduodenectomy: a multi-institutional study of 1302 patients. *Ann Surg*. 2012;256(3):529-37.

[18] Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008;454(7203):436-44.

[19] Marchesi F, Monti P, Leone BE, Zerbi A, Vecchi A, Piemonti L, Mantovani A, Allavena P. Increased survival, proliferation, and migration in metastatic human pancreatic tumor cells expressing functional CXCR4. *Cancer Res*. 2004;64(22): 8420-7.

[20] McKay CJ, Glen P, McMillan DC. Chronic inflammation and pancreatic cancer. *Best Pract Res Clin Gastroenterol*. 2008;22(1):65-73.

[21] Laird BJ, Scott AC, Colvin LA, McKeon AL, Murray GD, Fearon KC, Fallon MT. Cancer pain and its relationship to systemic inflammation: an exploratory study. *Pain*. 2011;152(2):460-3.

[22] Bar-Yosef S, Melamed R, Page GG, Shakhar G, Shakhar K, Ben-Eliyahu. Attenuation of the tumor-promoting effect of surgery by spinal blockade in rats. *Anesthesiology*. 2001;94:1066-73.

[23] Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. Their role in postoperative outcome. *Anesthesiology*. 1995;82(6):1474-506.

[24] Balcom JH 4th, Rattner DW, Warshaw AL, Chang Y, Fenandex-del Castillo C. Ten-year experience with 733 pancreatic resections: changing indications, older patients, and decreasing length of hospitalization. *Arch Surg*. 2001;136(4):391-8.

[25] Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, Hodgin MB, Sauter PK, Hruban RH, Riall TS, Schulick RD, Choti MA, Lillemoe KD, Yeo CJ. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. *J Gastrointest Surg*. 2006;10(6):1199-210.

[26] Matrisian L, Aizenberg R, Rosenzweig A. The alarming rise of pancreatic cancer deaths in the United States. http://www.pancan.org/section_research/reports/incidence_report.php. Accessed March 13, 2014.

[27] Cress RD, Yin D, Clarke L, Bold R, Holly EA. Survival among patients with adenocarcinoma of the pancreas: A population-based study (United States). *Cancer Causes Control*. 2006;17:403-9.

[28] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64(1):9-29.

[29] Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ. Cancer Statistics, 2006. *CA Cancer J Clin*. 2006;56:106-30.

[30] Hishinuma S, Ogata Y, Tamikawa M, Ozawa I, Hirabayashi K, Igarashi S. Patterns of recurrence after curative resection of pancreatic cancer, based on autopsy findings. *J Gastrointest Surg*. 2006;10(4):511-8.

[31] Gnerlich JL, Luka SR, Deshpande AD, Dubray BJ, Weir JS, Carpenter DH, Brunt EM, Strasberg SM, Hawkins WG, Linehan DC. Microscopic margins and patterns of treatment failure in resected pancreatic adenocarcinoma. *Arch Surg*. 2012;147(8):753-60.

[32] Sohal DP, Walsh RM, Ramanathan RK, Khorana AA. Pancreatic adenocarcinoma: treating a systemic disease with systemic therapy. *J Natl Cancer Inst*. 2014. Epub 2014 Feb 22.

[33] Scavonetto F, Yeoh TY, Umbreit EC, Weingarten TN, Gettman MT, Frank I, Boorjian SA, Karnes RJ, Schroeder DR, Rangel LJ, Hanson AC, Hofer RE, Sessler DI, Sprung J. Association between neuraxial analgesia, cancer progression, and mortality after radical prostatectomy: a large, retrospective matched cohort study. *Br J Anaesth.* 2013. Epub 2013 Dec 16.

[34] Holler JP, Ahibrandt J, Burkhardt E, Gruss M, Rohrig R, Knapheide J, Hecker A, Padberg W, Weigand MA. Peridural analgesia may affect long-term survival in patients with colorectal cancer after surgery (PACO-RAS-Study): an analysis of a cancer registry. *Ann Surg*. 2013;258(6):989-93.
[35] Christopherson R, James KE, Tableman M, Marshall P, Johnson FE. Long-term survival after colon cancer surgery: a variation associated with choice of anesthesia. *Anesth Analg*. 2008;107(1):325-32.
[36] Cummins KC 3rd, Xu F, Cummings LC, Cooper GS. A comparison of epidural analgesia and traditional pain management effects on survival and cancer recurrence after colectomy: a population-based study. *Anesthesiology*. 2012;116(4):797-806.
[37] Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, Brown DL, Heit JA, Mulroy MF, Rosenquist RW, Tryba M, Yuan CS. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med*. 2010;35:64-101.
[38] Finnerup NB, Sorenson L, Biering-Sorensen F, Johannesen IL, Jensen TS. Segmental hypersensitivity and spinothalamic function in spinal cord injury pain. *Ex Neurol*. 2007;207:139-149.
[39] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983 Jun;67(6):361-70.
[40] Ely, EW, Vanderbilt University. "Confusion Assessment Method for the ICU (CAM-ICU): The Complete Training Manual." Confusion Assessment Method for the ICU (CAM-ICU): The Complete Training Manual. March 1, 2014. Accessed December 14, 2016. http://www.icudelirium.org/docs/CAM_ICU_training.pdf.
[41] Mann C, Pouzeratte Y et al. Comparison of intravenous or epidural patient-controlled analgesia in the elderly after major abdominal surgery. *Anesthesiology*. 2000; 92:433-41.
[42] Fruhstorfer H, Lindblom U, Schmidt WC. Method for quantitative estimation of thermal thresholds in patients. *J Neurol Neurosurg Psychiatry*. 1976;39:1071-1075.
[43] Yarnitsky D, Sprecher E, Zaslansky R, Hemli JA. Heat pain thresholds: normative data and repeatability. *Pain.* 1995;60:329-332.
[44] Fruhstorfer H, Gross W, Selbmann O. von Frey hairs: new materials for a new design. *Eur J Pain.* 2001;5:341-342.
[45] Weinstein S, Fisher L, Richlin M, Weisinger M. Bibliography of sensory and perceptual deprivation, isolation, and related areas. *Percept Mot Skills*. 1968;26:Suppl:1119+.
[46] Baumgartner U, Magerl W, Klein T, Hopf HC, Treede RD. Neurogenic hyperalgesia versus painful hypoalgesia: two distinct mechanisms of neuropathic pain. *Pain.* 2002;96:141-151.
[47] Magerl W, Wilk SH, Treede RD. Secondary hyperalgesia and perceptual wind-up following intradermal injection of capsaicin in humans. *Pain.* 1998;74:257-268.
[48] Price DD, Hu JW, Dubner R, Gracely RH. Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. *Pain.* 1977;3:57-68.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,2
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	1,2,9
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	1,9
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	9
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7,8

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	___3,4_____
	6b	Explanation for choice of comparators	___N/A_____
Objectives	7	Specific objectives or hypotheses	____6,7_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___4-6_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____7_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	___4,5_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____4-6_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_____6-8_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____8_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____6_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____6-7_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____4-5,11____

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5-7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5-7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5-7
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6-7

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____7-8_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____7-8_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____N/A_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____7,8_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____8_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	____N/A_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____8_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____8_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____8_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____8_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___4-5_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____N/A_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____9_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____10_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____8_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____8_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____9_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____9_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____9_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__Supplemental_
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____5,6_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Epidurals in Pancreatic Resection Outcomes (E-PRO) study: protocol for a randomized controlled trial

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Epidurals in Pancreatic Resection Outcomes (E-PRO) study: protocol for a randomized controlled trial

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ABSTRACT

Introduction: Epidural analgesia provides an important synergistic method of pain control. In addition to reducing perioperative opioid consumption, the deliverance of analgesia into the epidural space, effectively creating a sympathetic blockade, has a multitude of additional potential benefits, from decreasing the incidence of postoperative delirium to reducing the development of persistent post-surgical pain (PPSP). Prior studies have also identified a correlation between the use of epidural analgesia and improved oncologic outcomes and survival. The aim of this study is to evaluate the effect of epidural analgesia in pancreatic operations on immediate postoperative outcomes, the development of PPSP, and oncologic outcomes in a prospective, single blind, randomized controlled trial.

Methods: The Epidurals in Pancreatic Resection Outcomes (E-PRO) study is a prospective, single-center, randomized controlled trial. 150 patients undergoing either pancreaticoduodenectomy or distal pancreatectomy will be randomized to receive an epidural bupivacaine infusion following anesthetic induction followed by continued epidural bupivacaine infusion postoperatively in addition to the institutional standardized pain regimen of hydromorphone patient-controlled analgesia, acetaminophen, and ketorolac (intervention group) or no epidural infusion and only the standardized postoperative pain regimen (control group). The primary outcome was the postoperative consumption of morphine or morphine-equivalents. Secondary outcomes include patient-reported postoperative pain numerical rating scores (NRS), trend and relative ratios of serum inflammatory markers (IL-1b, IL-6, TNF-a, IL-10), occurrence of postoperative delirium, development of PPSP as determined by quantitative sensory testing, and disease free and overall survival.

Ethics and dissemination: The E-PRO trial has been approved by the institutional review board. Recruitment began in May 2016 and will continue until the end of May 2018. Dissemination plans include presentations at scientific conferences and scientific publications.

Registration details: This study is registered at clinicaltrials.gov, NCT02681796 (last updated September 2016).

Trial registration number: NCT02681796 (last updated September 2016).

Strengths and Limitations: Strengths of this study include its design as a prospective randomized controlled trial and the length of longitudinal follow-up provided post-operatively. Limitations include the single-institutional nature of this study.

INTRODUCTION

Background and Rationale

Epidural Analgesia

The utilization of regional analgesia as a compliment to traditional pain management techniques has become an increasingly common practice at many institutions. Placed pre-operatively, epidural analgesia provides an important synergistic method of pain control post-operatively. In addition to its usefulness as a pain management adjunct, the deliverance of analgesia into the epidural space, effectively creating a sympathetic blockade, has a multitude of potential additional benefits.

Previous studies have examined the use of epidurals in abdominal surgeries with a small number of retrospective trials focusing on the use of epidurals in pancreatic resections[1]. While these retrospective studies demonstrated an improvement in patient-reported pain scores post-operatively, objective measures are still needed to quantify these improvements in pain control[2]. Prior studies have also highlighted a correlation between poor postoperative pain and the development of persistent post-surgical pain (PPSP)[3,4,5]. As epidural analgesia creates a sympathetic blockade, its intraoperative and postoperative use can mitigate the body's inflammatory response and reduce the activation of peripheral and central nervous systems pathways involved in the development of persistent pain syndromes[6]. Interleukin-1-beta (IL-1b), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-a) are three pro-inflammatory cytokines involved in the transition from acute pain states to chronic pain syndromes[7]. Interleukin-10 (IL-10) is an anti-inflammatory cytokine that helps modulate the body's stress response. IL-1b, IL-6, TNF-a, and IL-10, and the relative balance of the pro- and anti-inflammatory response, have all been implicated in nociceptive pathways and elevated levels have been found in chronic pain processes[8]. While our current understanding of the complex modulation pathways of pain is limited, circulating IL-6 has been demonstrated in the up-regulation of central and peripheral nociceptive receptors, thereby generating the perception of pain, and potentially establishing the link between acute and chronic pain[9,10]. This is of particular importance in our study population of patients with pancreatic diseases for whom adequate pain control is a critical factor in maintaining good quality of life[11,12].

In the immediate postoperative period, the use of epidural analgesia can improve other measures of patient recovery and healing, such as promoting gut motility and reducing the incidence of postoperative delirium. Along with reducing total opioid use, epidural analgesia produces a sympathectomy, allowing for dominance of the parasympathetic system, and further expediting the return of bowel function[13,14,15]. With delayed gastric emptying as one of the most common complications and reasons for readmission after pancreatic resections, this valuable benefit of epidural analgesia requires further investigation[16,17]. Delirium is another common postoperative complication that is associated with poor patient outcomes, including functional decline and death, and an effective prophylactic treatment remains to be identified. Through the effects of decreased intraoperative anesthetic requirement and postoperative opioid use, epidural analgesia may have a potential protective role against postoperative delirium.

The effect of epidural analgesia in suppressing the inflammatory cascade is of particular interest to the field of oncology. In certain types of cancers, including pancreatic, the oncogenic process generates an inflammatory environment that propagates the growth of malignant lesions and continued inflammatory conditions have been implicated in metastatic disease[18,19,20]. Pain

can further exacerbate systemic inflammation[21]. In additional to mitigating post-surgical pain, the sympathectomy resulting from epidural analgesia also reduces the body's overall inflammatory conditions[22,23]. This attenuation of the heightened postoperative inflammatory state of the body may provide an additional means of reducing progression of disease.

Pancreatic Diseases

With improved detection and imaging modalities, the incidence of pancreatic disease, and subsequently, pancreatic operations, has increased[24,25,26]. Pancreatic resection continues to be the primary surgical treatment in the treatment of many benign and malignant pancreatic diseases, with an estimated 4,000 operations performed annually in the United States [27]. However, the mean 5-year survival for malignant pancreatic disease remains the lowest of all cancers at 6%, with 70-85% of patients dying of systemic recurrence, not just local disease[28,29,30]. While the search continues for earlier screening methods, the development of adjunctive therapies to surgical resection remains the most promising target of efforts to improve outcomes in malignant diseases of the pancreas. In particular, in recent years, a paradigm shift has occurred in the study of pancreatic malignancies where pancreatic cancer is viewed as a systemic disease, even in early stages, requiring a systemic approach in additional to regional disease control[31,32,33,34]. In previous studies, primarily in prostate and colorectal malignancies, the use of epidural analgesia has suggested a correlation with improved oncologic outcomes and survival[35,36]. Given the role between inflammation and cancer development and recurrence, and the sympathetic blockade created by epidural analgesia, the significance of epidural analgesia in improving oncologic outcomes warrants continued investigation.

The aim of this study is to evaluate the effect of epidural analgesia in pancreatic operations on immediate postoperative outcomes, the development of PPSP, and oncologic outcomes in a prospective, single blind, randomized controlled trial.

METHODS AND ANALYSIS

Study Design

The Epidurals in Pancreatic Resection Outcomes (E-PRO) study is a prospective, single-center, randomized controlled trial. This study has been approved by the Institutional Review Board at Washington University in St. Louis.150 patients undergoing either pancreaticoduodenectomy or distal pancreatectomy will be randomized to receive an epidural infusion of 0.125% bupivacaine starting at 5 ml/hr (range of 5-8 ml/hr) following anesthetic induction followed by a standard epidural infusion of 0.1% bupivacaine at 4-6 ml/hr postoperatively in addition to the institutional standardized pain regimen of hydromorphone patient-controlled analgesia, IV acetaminophen, and ketorolac (intervention group) or no epidural infusion and only the standardized postoperative pain regimen (control group). Follow-up information will be collected from the medical record for up to 2 years post-operatively. The study design is outlined in Figure 1.

Eligibility Criteria

Patients 18 years old or older, who able to understand and sign an Institutional Review Board (IRB)-approved informed consent form, and who are undergoing either pancreaticoduodenectomy or distal pancreatectomy will be eligible for study inclusion. Patients will be excluded if they fulfill

any one of the following criteria: indication for operative intervention being chronic pancreatitis, currently on warfarin with an INR>1.4 or clopidogrel that cannot be discontinued 7 days prior to surgery, most recent INR prior to surgery >1.4, most recent platelet count prior to surgery <70,000/mcl, chronic opioid use as defined by use of more than 20mg oxycodone, or equivalent, daily, history of pre-existing neuropathic pain conditions, known medical history of significant psychiatric or cognitive impairment, or history of HIV, Hepatitis B, and/or Hepatitis C. Patients will be consented and enrolled during a clinic or preoperative evaluation appointment.

Baseline Assessment

Each study participant will be randomized into the control group with standard of care pain management regiment or the intervention group with the addition of epidural analgesia. Randomization will occur via a randomized number generation by the PI.

Patients will have the standard of care preoperative evaluation at the Barnes Jewish Hospital Center for Preoperative Assessment and Planning. Routine laboratory tests including complete blood count, comprehensive metabolic panel, and coagulation studies will be obtained and reviewed.

In patients receiving chronic antiplatelet or anticoagulant medications, the following procedure will be practiced to minimize the risk of bleeding (per American Society of Regional Anesthesia and Pain Medicine guidelines[37]):

Acetyl Salicylic acid (ASA, aspirin) or other NSAIDS may be continued prior to epidural catheter insertion. Clopidogrel use must be discontinued seven days before the procedure. The study participant's treating physician (e.g. surgeon, cardiologist, neurologist) will be consulted prior to the discontinuation of clopidogrel. Participants receiving warfarin will proceed with the following schedule: if INR < 1.4, subject may proceed with epidural catheter insertion. If INR >1.4, the participant's treating physician will be consulted whether warfarin can be discontinued until INR reaches <1.4, or the subject can be switched to Low Molecular Weight Heparin (LMWH), which can be discontinued 36 hours before catheter insertion. INR/PTT will be assessed on the day of epidural catheter insertion in all patients on anticoagulant (but not antiplatelet) therapy.

Study participants will undergo a complete medical history and physical examination, and the following baseline assessments:

1. Evaluation of hypersensitivity or dynamic mechanical allodynia to brush stimulation in the upper abdomen[38].
2. Quantitative sensory testing (QST) to assess warm and cold detection thresholds, heat and cold pain thresholds, mechanical detection and pain thresholds, presence of wind-up (enhanced temporal summation) to pinprick (Supplemental 1).
3. Screening for psychological risk factors for acute and chronic pain using Hospital Anxiety and Depression Scale (HADS)[39].
4. Baseline assessment for delirium using the 3D-CAM instrument (Supplemental 2).
5. Baseline assessment of serum inflammatory markers (IL-1b, IL-6, TNF-a, IL-10).

Interventions

Post-operatively, all patients will receive a standardized pain regimen including a hydromorphone PCA (initial settings of no bolus dose, 0.25 mg per demand dose, minimal interval dose time of 10 minutes), acetaminophen (1000 mg every 6 hours for 24 hours), and ketorolac (15 mg every 6 hours for 72 hours) per surgeon's preference. Study group patients will have an epidural bupivacaine infusion beginning in the operating room.

An epidural infusion of 0.125% bupivacaine starting at 5 ml/hr (range of 5-8 ml/hr) will be started after induction of anesthesia. Epidural narcotic consisting of fentanyl 50 mcg will be administered with sterile precaution by the anesthesia provider before starting the epidural infusion. Epidural boluses of 0.125% bupivacaine may be administered as guided clinically. A phenylephrine infusion can be used to maintain adequate blood pressure maintaining mean arterial pressures (MAP) above 60 mmHg. The epidural infusion can be paused if vasopressor requirements exceed 1 mcg/kg/min of phenylephrine or 0.1 mcg/kg/min of norepinephrine. The epidural infusion is to be paused if hemodynamics become unstable, either due to excessive blood loss or MAP consistently below 60 mmHg. The epidural infusion can be resumed when hemodynamics are stable.

The bupivacaine 0.125% epidural infusion is to be discontinued in the OR at the end of surgery and a standard epidural infusion of 0.1% bupivacaine at 4-6 ml/hr will be started in the PACU. The epidural infusion is followed up by an Acute Pain Service in the postoperative period that will titrate the infusion based on the patients' self-reported pain scores and MAP values.

Outcomes

Primary Outcomes

The primary study outcome is the consumption of morphine or morphine-equivalent in patients undergoing pancreatic resections in the control group compared with the study group. Each subject's morphine or morphine-equivalent consumption will be assessed every 24 hours. All subjects will be assessed daily during their postoperative inpatient admission by a trained member of the Acute Pain Service who is blinded to the treatment arm of the study.

Secondary Outcomes

Study team members blinded to the treatment group of the patient will assess all secondary outcomes. Various measures of patient recovery and healing in the initial postoperative period will be evaluated, including visual analog scores (VAS), intravenous fluid requirements, anti-emetic doses, and return of bowel function. Serum inflammatory markers will be evaluated serially, preoperatively on day of surgery, three hours after the start of surgical incision in the operating room, on postoperative day 2, and at the initial postoperative visit 2-6 weeks after surgery. Postoperative delirium assessments will be performed when patients can be aroused sufficiently in order to be assessed for delirium (Richmond Agitation-Sedation Scale (RASS) > -4). Each patient will be assessed for delirium on postoperative day 2 as postoperative delirium typically first manifests 24-96 hours after surgery. For non-verbal patients the CAM-ICU instrument will be used and for verbal patients, the 3D-CAM instrument will be used[40]. As delirium is a fluctuating disorder and can be missed with sporadic delirium assessments, a

structured method of chart review will be used to complement the clinical assessments. This combined approach (3D-CAM interview or CAM-ICU plus chart review) increases the sensitivity and retains specificity in detecting incident delirium. The trial staff has undergone formal training in clinical delirium assessment and on the chart review methodology.

Patients will be seen for their initial postoperative weeks at 2-6 weeks after hospital discharge and will undergo repeat PPSP evaluation at that time.

Patients will continue to be followed in clinic for 2 years postoperatively with laboratory and radiologic evaluation as deemed appropriate by the primary surgeon. Patients will be followed for tumor recurrence and overall survival. Data will be collected directly from subject's medical record; no study-specific procedures will be implemented at follow up visits.

Sample Size

For purposes of sample size estimation, total morphine consumption in the first 72 hours after surgery is the primary outcome of the study. Based on our prior experience, sample size estimation will be based on the following assumptions[41]: Expected morphine consumption is 30 milligrams intraoperatively, 30 mg on postoperative day 1 (POD1), 20 mg on POD2 and 10 mg on POD3. Therefore, expected total morphine consumption in the first 72 hours is, on average, 80 mg. Then, assuming that the standard deviation of morphine consumption is 30 mg, that a 20 mg difference in morphine consumption between groups is a clinically meaningful reduction of opioid use and assuming normal distribution of morphine consumption in both patient groups, the proposed sample size for a = 0.05 and b = 0.2 would be 37 patients per group (74 patients in total). However, we propose to increase the sample size of the study to 150 total patients to account for patients lost to follow-up, inability to complete the scheduled pancreatic resection, data errors, and other un-anticipated study problems.

Recruitment

Participants will be recruited primarily through the Washington University Hepatobiliary-Pancreatic Surgery clinics. Subjects will be given verbal (initially) and then written descriptions of the study aims, procedures, risks, and benefits, and will be required to give written informed consent. A member of the investigative team provides all study descriptions, informed consent, and answers all questions. No deception is required for the purposes of this study. All subjects will be aware of the randomization used in this study to either the control or intervention group. Subjects are informed verbally and in writing that participation is voluntary and they may refuse to participate and may withdraw from the study at any time without penalty.

Allocation

Participants will be randomized in a 1:1 ratio into the control group with standard of care pain management regimen or the intervention group with the addition of epidural analgesia. Randomization will occur via randomized number generation.

This is a single-blind study. Patients and the primary investigative team will be aware of the randomization. However, all study members performing data collection will be blinded to the randomization.

Data Analysis and Management

Data analysis for this study will focus on the comparison of patient outcomes (postoperative morphine/morphine-equivalent consumption, measures of postoperative recovery, inflammatory markers, 3D-CAM/CAM-ICU assessments, QST) between the intervention and control study groups. Based on data distribution, continuous variables will be compared between the two groups using student's t test or the Mann Whitney U test as appropriate. When appropriate, significance of findings will be adjusted for multiple comparisons using the Bonferroni correction method.

The Center for Biomedical Informatics at Washington University will be used as the central location for data collection and management. Since 2008, Washington University has hosted Research Electronic Data Capture (REDCap), a secure, web-based application for building and storing online research and clinical trial databases. The REDCap servers are securely housed in an on-site limited access data center managed by the Center for Biomedical Informatics at Washington University. All web-based information transmission is encrypted and all data are stored on a private firewall protected network. All users are assigned individual user IDs and passwords and individual access is restricted on a role-specific basis. REDCap was developed specifically around HIPAA guidelines and is also implemented and maintained in accordance with institutional security guidelines.

Monitoring

The study team will monitor all study participants for adverse events. The principal investigator will report all unanticipated problems or adverse events, all conditions of noncompliance, and any new information that may affect the continued or current enrollment of study participants to the IRB. All events will be reported to the IRB within 10 working days of the event or of notification of the principal investigator of the event. The death of a study participant must be reported to the IRB within 1 working day of the event or of notification of the principal investigator of the event.

The specific monitoring plan for this investigation is commensurate with the risks and the size and complexity of the investigations planned. The potential risks are attributable to performing insertion of the epidural catheter and the use of bupivacaine for neuraxial analgesia. Based on these considerations, the monitoring plan involves engaging a colleague from the Department of Anesthesiology not involved in the study to serve in a monitoring capacity. Based on the small size and relatively low risks nature of the protocol, only a third person (the colleague), rather than a full Data Safety Monitoring Board will be used. The colleague will be an anesthesiologist knowledgeable in the risks associated with nerve blocks and local anesthetic administration. This individual will review the annual summary of adverse events. In addition, this colleague will review all reports of a Serious Adverse Event, or an Unexpected Adverse Event.

ETHICS AND DISSEMINATION

Ethics Approval and Consent

The E-PRO trial was provided ethical approval by the Washington University in St. Louis's Institutional Review Board which serves Washington University and Barnes-Jewish Hospital. Study recruitment and enrollment began in May 2016 and will continue through the end of 2017. Potential study participants will be given verbal and then written descriptions of the study aims, procedures, risks, and benefits, and written informed consent will be obtained for all participants. All participants are informed verbally and in writing that participation is voluntary and they may refuse to participate and may withdraw from the study at any time without penalty.

Confidentiality

Only the investigators and research team will have access to any protected health information of study participants and any study data. All subjects will be assigned a study ID number. All study data and samples will be coded with the assigned study ID number. A key to the code linking code numbers to patient names will be kept at a separate location, under lock and key; this link will be destroyed at the conclusion of this study. All data will be recorded by a member of the research team and will be stored in a password-protected electronic database stored on the departmental network drive. Study data will be not be entered into participants' medical records.

Dissemination

Dissemination plans include presentations at scientific conferences and scientific publications.

CONCLUSIONS

This trial investigates a wide spectrum of potential benefits to patients undergoing pancreatic resection. During the initial postoperative period, the use of epidural analgesia can aid in improving postoperative pain control, decreasing opioid consumption, reducing the incidence of delirium, and expediting recovery. In addition to improving immediate post-surgical pain control, epidural analgesia may reduce the development of persistent post-surgical pain, which can persist for weeks to years after surgery. Lastly, epidural analgesia can help reduce the body's stress response to a major operation, which has been linked to malignant progression and spread. Based on this trial, we seek to establish the role of epidural analgesia as part of the standard of care in future patients undergoing pancreatic operations.

Authors' Contributions

LMP and MMB are the primary authors of the E-PRO protocol. Their contributions include conceptualizing the study design, drafting and editing the protocol, and creating the electronic database REDCap used for data collection. WGH contributed to the E-PRO protocol by editing the protocol and recruiting patients for enrollment. SH contributed to the E-PRO protocol by conceptualizing the study design, drafting and editing the protocol, and supervising data collection. LW contributed to the E-PRO protocol by editing the protocol, recruiting patients, and collecting data. MK contributed to the E-PRO protocol by recruiting patients and collecting data. KF contributed to the E-PRO protocol and editing the protocol, creating the electronic

database REDCap, coordinating patient enrollment and data collection. RAS contributed to the E-PRO protocol by conceptualizing the study design and editing the protocol. All authors including LMP, WGH, SH, LW, MK, KF, RAS, and MMB have critically revised the E-PRO protocol and approved the final version. All authors agree to be accountable for the accuracy and integrity of all aspects of the E-PRO trial.

Funding Statement
This works was supported by the Foundation for Barnes-Jewish Hospital Project Award grant number 8083-88.

Competing Interests Statement
None

FIGURE LEGEND

Figure 1. Study design.

SUPPLEMENTAL FILES

Supplemental 1. Quantitative sensory testing (QST) protocol.

Supplemental 2. 3D-CAM assessment.

References

[1] Park WY, Thompson JS, Lee KK. Effect of epidural anesthesia and analgesia on perioperative outcome: a randomized, controlled Veterans Affairs cooperative study. *Ann Surg*. 2001;234:560-571.

[2] Choi DX, Schoeniger LO. For patients undergoing pancreatoduodenectomy, epidural anesthesia and analgesia improves pain but increases rates of intensive care unit admission and alterations in analgesics. *Pancreas*. 2010;39(4):492-7.

[3] Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet*. 2006;367(9522):1618-25.

[4] Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. *Expert Rev Neurother*. 2009;9(5):723-44.

[5] Pogatzki-Zahn EM, Schnabel A, Zahn PK. Room for improvement: unmet needs in postoperative pain management. *Expert Rev Neurother*. 2012;12(5):587-600.

[6] Zhang JM, An J. Cytokines, inflammation, and pain. *Int Anesthesiol Clin*. 2007;45(2):27-37.

[7] DeVon HA, Piano MR, Rosenfeld AG, Hoppensteadt DA. The association of pain with protein inflammatory biomarkers: a review of the literature. *Nurs Res*. 2014;63(1):61-62.

[8] Uceyler N, Eberle T, Rolke R, Birklein F, Sommer C. Differential expression patterns of cytokines in complex regional pain syndrome. *Pain*. 2007;132(1-2):195-205.

[9] De Jongh RF, Vissers KC, Meert TF, Booij LH, De Deyne CS, Heylen RJ. The role of interleukin-6 in nociception and pain. *Anesth Analg*. 2003;96(4):1096-103.

[10] Woolf CJ, Costigan M. Transcriptional and posttranslational plasticity and the generation of inflammatory pain. *Proc Natl Acad Sci U S A*. 1999;96(4):7723-30.

[11] Burger V, D'Olimpio JT. Improving quality of life through pain control. *Clin J Oncol Nurs*. 2013;17(2):117-8.

[12] Chan C, Franssen B, Dominguez I, Ramirez-Del Val A, Uscanga LF, Compuzano M. Impact on quality of life after pancreatoduodenectomy: a prospective study comparing preoperative and postoperative scores. *J Gastrointest Surg*. 2012;16(7):1341-6.

[13] Carroll J, Alavi K. Pathogenesis and management of postoperative ileus. *Clin Colon Rectal Surg*. 2009;22(1):47-50.

[14] Leslie JB, Viscusi ER, Pergolizzi JV Jr, Panchal SJ. Anesthetic routines: the anesthesiologist's role in GI recovery and postoperative ileus. *Adv Prev Med*. 2011;2011: 976904. Epub 2010 Dec 29.

[15] Person B, Wexner SD. The management of postoperative ileus. *Curr Probl Surg*. 2006;43(1):6-65.

[16] Emick DM, Riall TS, Cameron JL, Winter JM, Lillemoe KD, Coleman J, Sauter PK, Yeo CJ. Hospital readmission after pancreaticoduodenectomy. *J Gastrointest Surg*. 2006;10(9):1243-52.

[17] Ahmad SA, Edwards MJ, Sutton JM, Grewal SS, Hansenman DJ, Maithel SK, Patel SH, Bentram DJ, Weber SM, Cho CS, Winslow ER, Scoggins CR, Martin RC, Kim HJ, Baker JJ, Merchant NB, Parikh AA, Kooby DA. Factors influencing readmission after pancreaticoduodenectomy: a multi-institutional study of 1302 patients. *Ann Surg*. 2012;256(3):529-37.

[18] Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008;454(7203):436-44.

[19] Marchesi F, Monti P, Leone BE, Zerbi A, Vecchi A, Piemonti L, Mantovani A, Allavena P. Increased survival, proliferation, and migration in metastatic human pancreatic tumor cells expressing functional CXCR4. *Cancer Res*. 2004;64(22): 8420-7.

[20] McKay CJ, Glen P, McMillan DC. Chronic inflammation and pancreatic cancer. *Best Pract Res Clin Gastroenterol*. 2008;22(1):65-73.

[21] Laird BJ, Scott AC, Colvin LA, McKeon AL, Murray GD, Fearon KC, Fallon MT. Cancer pain and its relationship to systemic inflammation: an exploratory study. *Pain*. 2011;152(2):460-3.

[22] Bar-Yosef S, Melamed R, Page GG, Shakhar G, Shakhar K, Ben-Eliyahu. Attenuation of the tumor-promoting effect of surgery by spinal blockade in rats. *Anesthesiology*. 2001;94:1066-73.

[23] Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. Their role in postoperative outcome. *Anesthesiology*. 1995;82(6):1474-506.

[24] Balcom JH 4th, Rattner DW, Warshaw AL, Chang Y, Fenandex-del Castillo C. Ten-year experience with 733 pancreatic resections: changing indications, older patients, and decreasing length of hospitalization. *Arch Surg*. 2001;136(4):391-8.

[25] Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, Hodgin MB, Sauter PK, Hruban RH, Riall TS, Schulick RD, Choti MA, Lillemoe KD, Yeo CJ. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. *J Gastrointest Surg*. 2006;10(6):1199-210.

[26] Matrisian L, Aizenberg R, Rosenzweig A. The alarming rise of pancreatic cancer deaths in the United States. http://www.pancan.org/section_research/reports/incidence_report.php. Accessed March 13, 2014.

[27] Cress RD, Yin D, Clarke L, Bold R, Holly EA. Survival among patients with adenocarcinoma of the pancreas: A population-based study (United States). *Cancer Causes Control*. 2006;17:403-9.

[28] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64(1):9-29.

[29] Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ. Cancer Statistics, 2006. *CA Cancer J Clin*. 2006;56:106-30.

[30] Hishinuma S, Ogata Y, Tamikawa M, Ozawa I, Hirabayashi K, Igarashi S. Patterns of recurrence after curative resection of pancreatic cancer, based on autopsy findings. *J Gastrointest Surg*. 2006;10(4):511-8.

[31] Gnerlich JL, Luka SR, Deshpande AD, Dubray BJ, Weir JS, Carpenter DH, Brunt EM, Strasberg SM, Hawkins WG, Linehan DC. Microscopic margins and patterns of treatment failure in resected pancreatic adenocarcinoma. *Arch Surg*. 2012;147(8):753-60.

[32] Sohal DP, Walsh RM, Ramanathan RK, Khorana AA. Pancreatic adenocarcinoma: treating a systemic disease with systemic therapy. *J Natl Cancer Inst*. 2014. Epub 2014 Feb 22.

[33] Scavonetto F, Yeoh TY, Umbreit EC, Weingarten TN, Gettman MT, Frank I, Boorjian SA, Karnes RJ, Schroeder DR, Rangel LJ, Hanson AC, Hofer RE, Sessler DI, Sprung J. Association between neuraxial analgesia, cancer progression, and mortality after radical prostatectomy: a large, retrospective matched cohort study. *Br J Anaesth.* 2013. Epub 2013 Dec 16.

[34] Holler JP, Ahibrandt J, Burkhardt E, Gruss M, Rohrig R, Knapheide J, Hecker A, Padberg W, Weigand MA. Peridural analgesia may affect long-term survival in patients with colorectal cancer after surgery (PACO-RAS-Study): an analysis of a cancer registry. *Ann Surg*. 2013;258(6):989-93.

[35] Christopherson R, James KE, Tableman M, Marshall P, Johnson FE. Long-term survival after colon cancer surgery: a variation associated with choice of anesthesia. *Anesth Analg*. 2008;107(1):325-32.

[36] Cummins KC 3rd, Xu F, Cummings LC, Cooper GS. A comparison of epidural analgesia and traditional pain management effects on survival and cancer recurrence after colectomy: a population-based study. *Anesthesiology*. 2012;116(4):797-806.

[37] Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, Brown DL, Heit JA, Mulroy MF, Rosenquist RW, Tryba M, Yuan CS. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med*. 2010;35:64-101.

[38] Finnerup NB, Sorenson L, Biering-Sorensen F, Johannesen IL, Jensen TS. Segmental hypersensitivity and spinothalamic function in spinal cord injury pain. *Ex Neurol*. 2007;207:139-149.

[39] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983 Jun;67(6):361-70.

[40] Ely, EW, Vanderbilt University. "Confusion Assessment Method for the ICU (CAM-ICU): The Complete Training Manual." Confusion Assessment Method for the ICU (CAM-ICU): The Complete Training Manual. March 1, 2014. Accessed December 14, 2016. http://www.icudelirium.org/docs/CAM_ICU_training.pdf.

[41] Mann C, Pouzeratte Y et al. Comparison of intravenous or epidural patient-controlled analgesia in the elderly after major abdominal surgery. *Anesthesiology*. 2000; 92:433-41.

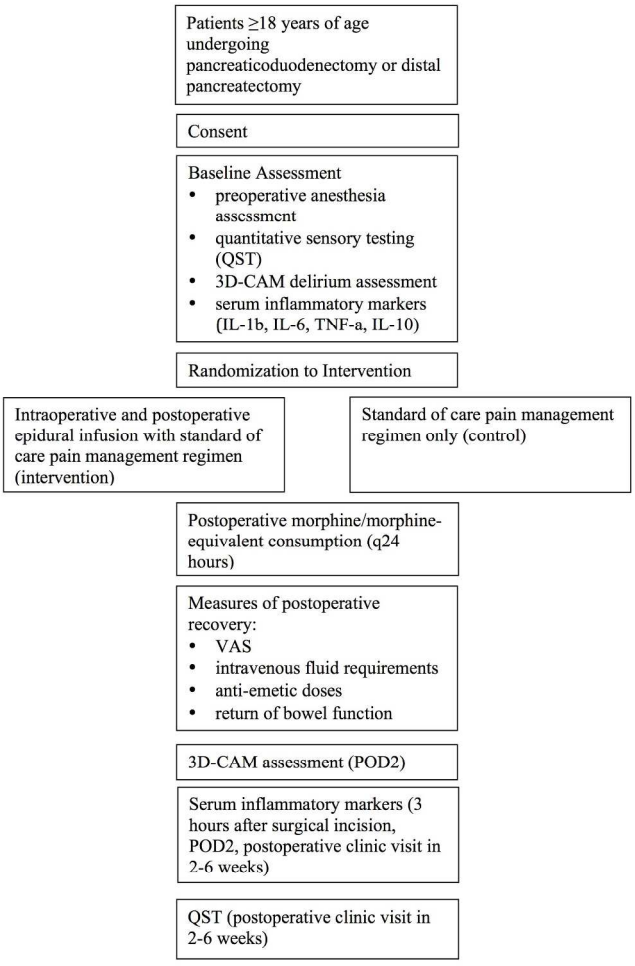

Figure 1. Study design

215x279mm (300 x 300 DPI)

Supplemental 1. Quantitative sensory testing (QST) protocol.

Quantitative sensory testing will be performed in the main assessment area on the abdomen, in close proximity to the surgical incision.

A description of the QST procedures follows:

Thermal detection and thermal pain thresholds
Equipment: The Thermal Sensory Analyzer (TSA-II or PATHWAY platform - Medoc, Ramat Yishai, Israel) will be used to determine thermal detection and pain thresholds. This equipment is used globally for functional assessment of pain and temperature-conducting nerve fibers (C and A-delta fibers).
Method and Background: Using the thermal sensory analyzer, cold and warm detection thresholds (CDT and WDT, respectively), as well as cold and heat pain thresholds (CPT and HPT, respectively) will be determined. The thermode with contact area of 9.0 cm^2 is applied to the tested site, and all thresholds are determined by continuous ramping of temperature from 32°C baseline temperature by 1°C/s until the subject presses the 'stop' button. Cut-off temperatures are 0°C and 50°C, to minimize thermal damage to the skin. The baseline temperature to which the thermode returns before each test is 32°C. The average threshold is calculated from three measurements in each area.

Determination of mechanical detection threshold (MDT)
Equipment: A set of standardised von Frey filaments (#1.65, #2.35, #2.44, #2.83, #3.22, #3.61, #3.84, #4.08, #4.17, #4.31, #4.74, #4.93, #5.07, #5.18, #5.46, #5.88, #6.10, #6.45, 6.65. The contact area of the filaments with the skin is of uniform size (<1 mm^2) and texture.

Methods and Background: Standardised von Frey filaments will be used in a modified "method of limits" manner using 3 series of increasing and decreasing stimulus intensities to determine the geometric average as the tactile detection threshold of the affected and unaffected skin areas.

Von Frey filaments of different stimulus intensities are used to determine the tactile detection thresholds. A #5.07 filament (eliciting 10 gram force)* is applied first, followed by filaments of consecutively lower intensity until the patient cannot detect the stimulus being applied. This respective force represents the first threshold value. The order in which the stimuli are applied is then reversed and stimuli of consecutively greater intensity are applied until sensation is detected (this intensity becomes the second value). Again filaments with decreasing intensity are applied until in total 3 upper and lower values of detection are fulfilled from which the mechanical detection threshold can be determined.

* In case the first von Frey filament (#5.07) is not detected, the next highest intensity filament which can be detected must be used as a starting intensity. However, the relevant force of this stimulus is not documented. Filaments with consecutively lower intensity are applied until the patient cannot detect the stimulus being applied. The procedure is followed as above; until in total 3 upper and lower values of detection are fulfilled from which the mechanical detection threshold can be determined.

Determination of mechanical pain thresholds (MPT)

Equipment: Same as for MDT determination.
Methods and Background:
Standardised von Frey filaments will be used in a modified "method of limits" manner using 3 series of increasing stimulus intensities to determine the average mechanical pain threshold of the affected and unaffected skin areas.
Beginning with an applied force of 8mN, stimuli increase in intensity until the sensation induced by increased pressure can be described as 'painful'. The corresponding force is used to represent the first MPT value. The procedure is then repeated a total of 3 times and until a total of 3 values are obtained, from which the mean mechanical pain threshold can be determined.

Determination of wind-up ratio (WUR)
Equipment: A pinprick stimulus with standardised intensity (#6.10 von Frey filament, approx. 98 gram) and a flat contact area of 0.25mm diameter.
Methods and Background: In this test a pinprick) is first applied singularly. After that a series of 10 identical pinprick stimuli are applied with a frequency of 1 s^{-1} within an area of 1 cm^2.
Immediately following the single stimulus and series of stimuli, an evaluation of the sensation must be provided according to NRS (0-10, '0': 'no pain', '10': 'worst pain imaginable'). A ratio is calculated using these values. This procedure shall be repeated twice. A geometric average of the 'wind-up' is calculated from the two ratios.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,2
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	1,2,9
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	1,9
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	9
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7,8

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	___3,4_____
	6b	Explanation for choice of comparators	___N/A_____
Objectives	7	Specific objectives or hypotheses	____6,7_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___4-6_____

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____7_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	___4,5_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____4-6_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_____6-8_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____8_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____6_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____6-7_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____4-5,11____

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____7_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____7_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____5_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____5-7_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____5_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____5-7_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____5-7_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____5-7_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____6-7_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____7-8_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____7-8_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____N/A_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____7,8_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____8_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	____N/A_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____8_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____8_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____8_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____8_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___4-5_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____N/A_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____9_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____10_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____8_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____8_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____9_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____9_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____9_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__Supplemental_
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____5,6_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Epidurals in Pancreatic Resection Outcomes (E-PRO) study: protocol for a randomized controlled trial

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ABSTRACT

Introduction: Epidural analgesia provides an important synergistic method of pain control. In addition to reducing perioperative opioid consumption, the deliverance of analgesia into the epidural space, effectively creating a sympathetic blockade, has a multitude of additional potential benefits, from decreasing the incidence of postoperative delirium to reducing the development of persistent post-surgical pain (PPSP). Prior studies have also identified a correlation between the use of epidural analgesia and improved oncologic outcomes and survival. The aim of this study is to evaluate the effect of epidural analgesia in pancreatic operations on immediate postoperative outcomes, the development of PPSP, and oncologic outcomes in a prospective, single blind, randomized controlled trial.

Methods: The Epidurals in Pancreatic Resection Outcomes (E-PRO) study is a prospective, single-center, randomized controlled trial. 150 patients undergoing either pancreaticoduodenectomy or distal pancreatectomy will be randomized to receive an epidural bupivacaine infusion following anesthetic induction followed by continued epidural bupivacaine infusion postoperatively in addition to the institutional standardized pain regimen of hydromorphone patient-controlled analgesia, acetaminophen, and ketorolac (intervention group) or no epidural infusion and only the standardized postoperative pain regimen (control group). The primary outcome was the postoperative opioid consumption, measured in morphine or morphine-equivalents. Secondary outcomes include patient-reported postoperative pain numerical rating scores (NRS), trend and relative ratios of serum inflammatory markers (IL-1b, IL-6, TNF-a, IL-10), occurrence of postoperative delirium, development of PPSP as determined by quantitative sensory testing, and disease free and overall survival.

Ethics and dissemination: The E-PRO trial has been approved by the institutional review board. Recruitment began in May 2016 and will continue until the end of May 2018. Dissemination plans include presentations at scientific conferences and scientific publications.

Registration details: This study is registered at clinicaltrials.gov, NCT02681796 (last updated September 2016).

Trial registration number: NCT02681796 (last updated September 2016).

Strengths and Limitations: Strengths of this study include its design as a prospective randomized controlled trial and the length of longitudinal follow-up provided post-operatively. Limitations include the single-institutional nature of this study.

INTRODUCTION

Background and Rationale

Epidural Analgesia

The utilization of regional analgesia as a compliment to traditional pain management techniques has become an increasingly common practice at many institutions. Placed pre-operatively, epidural analgesia provides an important synergistic method of pain control post-operatively. In addition to its usefulness as a pain management adjunct, the deliverance of analgesia into the epidural space, effectively creating a sympathetic blockade, has a multitude of potential additional benefits.

Previous studies have examined the use of epidurals in abdominal surgeries with a small number of retrospective trials focusing on the use of epidurals in pancreatic resections[1]. While these retrospective studies demonstrated an improvement in patient-reported pain scores post-operatively, objective measures are still needed to quantify these improvements in pain control[2]. Prior studies have also highlighted a correlation between poor postoperative pain and the development of persistent post-surgical pain (PPSP)[3,4,5]. As epidural analgesia creates a sympathetic blockade, its intraoperative and postoperative use can mitigate the body's inflammatory response and reduce the activation of peripheral and central nervous systems pathways involved in the development of persistent pain syndromes[6]. Interleukin-1-beta (IL-1b), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-a) are three pro-inflammatory cytokines involved in the transition from acute pain states to chronic pain syndromes[7]. Interleukin-10 (IL-10) is an anti-inflammatory cytokine that helps modulate the body's stress response. IL-1b, IL-6, TNF-a, and IL-10, and the relative balance of the pro- and anti-inflammatory response, have all been implicated in nociceptive pathways and elevated levels have been found in chronic pain processes[8]. While our current understanding of the complex modulation pathways of pain is limited, circulating IL-6 has been demonstrated in the up-regulation of central and peripheral nociceptive receptors, thereby generating the perception of pain, and potentially establishing the link between acute and chronic pain[9,10]. This is of particular importance in our study population of patients with pancreatic diseases for whom adequate pain control is a critical factor in maintaining good quality of life[11,12].

In the immediate postoperative period, the use of epidural analgesia can improve other measures of patient recovery and healing, such as promoting gut motility and reducing the incidence of postoperative delirium. Along with reducing total opioid use, epidural analgesia produces a sympathectomy, allowing for dominance of the parasympathetic system, and further expediting the return of bowel function[13,14,15]. With delayed gastric emptying as one of the most common complications and reasons for readmission after pancreatic resections, this valuable benefit of epidural analgesia requires further investigation[16,17]. Delirium is another common postoperative complication that is associated with poor patient outcomes, including functional decline and death, and an effective prophylactic treatment remains to be identified. Through the effects of decreased intraoperative anesthetic requirement and postoperative opioid use, epidural analgesia may have a potential protective role against postoperative delirium.

The effect of epidural analgesia in suppressing the inflammatory cascade is of particular interest to the field of oncology. In certain types of cancers, including pancreatic, the oncogenic process generates an inflammatory environment that propagates the growth of malignant lesions and continued inflammatory conditions have been implicated in metastatic disease[18,19,20]. Pain

can further exacerbate systemic inflammation[21]. In additional to mitigating post-surgical pain, the sympathectomy resulting from epidural analgesia also reduces the body's overall inflammatory conditions[22,23]. This attenuation of the heightened postoperative inflammatory state of the body may provide an additional means of reducing progression of disease.

Pancreatic Diseases

With improved detection and imaging modalities, the incidence of pancreatic disease, and subsequently, pancreatic operations, has increased[24,25,26]. Pancreatic resection continues to be the primary surgical treatment in the treatment of many benign and malignant pancreatic diseases, with an estimated 4,000 operations performed annually in the United States [27]. However, the mean 5-year survival for malignant pancreatic disease remains the lowest of all cancers at 6%, with 70-85% of patients dying of systemic recurrence, not just local disease[28,29,30]. While the search continues for earlier screening methods, the development of adjunctive therapies to surgical resection remains the most promising target of efforts to improve outcomes in malignant diseases of the pancreas. In particular, in recent years, a paradigm shift has occurred in the study of pancreatic malignancies where pancreatic cancer is viewed as a systemic disease, even in early stages, requiring a systemic approach in additional to regional disease control[31,32,33,34]. In previous studies, primarily in prostate and colorectal malignancies, the use of epidural analgesia has suggested a correlation with improved oncologic outcomes and survival[35,36]. Given the role between inflammation and cancer development and recurrence, and the sympathetic blockade created by epidural analgesia, the significance of epidural analgesia in improving oncologic outcomes warrants continued investigation.

The aim of this study is to evaluate the effect of epidural analgesia in pancreatic operations on immediate postoperative outcomes, the development of PPSP, and oncologic outcomes in a prospective, single blind, randomized controlled trial.

METHODS AND ANALYSIS

Study Design

The Epidurals in Pancreatic Resection Outcomes (E-PRO) study is a prospective, single-center, randomized controlled trial. This study has been approved by the Institutional Review Board at Washington University in St. Louis.150 patients undergoing either pancreaticoduodenectomy or distal pancreatectomy will be randomized to receive an epidural infusion of 0.125% bupivacaine starting at 5 ml/hr (range of 5-8 ml/hr) following anesthetic induction followed by a standard epidural infusion of 0.1% bupivacaine at 4-6 ml/hr postoperatively in addition to the institutional standardized pain regimen of hydromorphone patient-controlled analgesia, IV acetaminophen, and ketorolac (intervention group) or no epidural infusion and only the standardized postoperative pain regimen (control group). Follow-up information will be collected from the medical record for up to 2 years post-operatively. The study design is outlined in Figure 1.

Eligibility Criteria

Patients 18 years old or older, who able to understand and sign an Institutional Review Board (IRB)-approved informed consent form, and who are undergoing either pancreaticoduodenectomy or distal pancreatectomy will be eligible for study inclusion. Patients will be excluded if they fulfill

any one of the following criteria: indication for operative intervention being chronic pancreatitis, currently on warfarin with an INR>1.4 or clopidogrel that cannot be discontinued 7 days prior to surgery, most recent INR prior to surgery >1.4, most recent platelet count prior to surgery <70,000/mcl, chronic opioid use as defined by use of more than 20mg oxycodone, or equivalent, daily, history of pre-existing neuropathic pain conditions, known medical history of significant psychiatric or cognitive impairment, or history of HIV, Hepatitis B, and/or Hepatitis C. Patients will be consented and enrolled during a clinic or preoperative evaluation appointment.

Baseline Assessment

Each study participant will be randomized into the control group with standard of care pain management regiment or the intervention group with the addition of epidural analgesia. Randomization will occur via a randomized number generation by the PI.

Patients will have the standard of care preoperative evaluation at the Barnes Jewish Hospital Center for Preoperative Assessment and Planning. Routine laboratory tests including complete blood count, comprehensive metabolic panel, and coagulation studies will be obtained and reviewed.

In patients receiving chronic antiplatelet or anticoagulant medications, the following procedure will be practiced to minimize the risk of bleeding (per American Society of Regional Anesthesia and Pain Medicine guidelines[37]):

Acetyl Salicylic acid (ASA, aspirin) or other NSAIDS may be continued prior to epidural catheter insertion. Clopidogrel use must be discontinued seven days before the procedure. The study participant's treating physician (e.g. surgeon, cardiologist, neurologist) will be consulted prior to the discontinuation of clopidogrel. Participants receiving warfarin will proceed with the following schedule: if INR < 1.4, subject may proceed with epidural catheter insertion. If INR >1.4, the participant's treating physician will be consulted whether warfarin can be discontinued until INR reaches <1.4, or the subject can be switched to Low Molecular Weight Heparin (LMWH), which can be discontinued 36 hours before catheter insertion. INR/PTT will be assessed on the day of epidural catheter insertion in all patients on anticoagulant (but not antiplatelet) therapy.

Study participants will undergo a complete medical history and physical examination, and the following baseline assessments:

1. Evaluation of hypersensitivity or dynamic mechanical allodynia to brush stimulation in the upper abdomen[38].
2. Quantitative sensory testing (QST) to assess warm and cold detection thresholds, heat and cold pain thresholds, mechanical detection and pain thresholds, presence of wind-up (enhanced temporal summation) to pinprick (Supplemental 1).
3. Screening for psychological risk factors for acute and chronic pain using Hospital Anxiety and Depression Scale (HADS)[39].
4. Baseline assessment for delirium using the 3D-CAM instrument[40].
5. Baseline assessment of serum inflammatory markers (IL-1b, IL-6, TNF-a, IL-10).

Interventions

Post-operatively, all patients will receive a standardized pain regimen including a hydromorphone PCA (initial settings of no bolus dose, 0.25 mg per demand dose, minimal interval dose time of 10 minutes), acetaminophen (1000 mg every 6 hours for 24 hours), and ketorolac (15 mg every 6 hours for 72 hours) per surgeon's preference. Study group patients will have an epidural bupivacaine infusion beginning in the operating room.

An epidural infusion of 0.125% bupivacaine starting at 5 ml/hr (range of 5-8 ml/hr) will be started after induction of anesthesia. Epidural narcotic consisting of fentanyl 50 mcg will be administered with sterile precaution by the anesthesia provider before starting the epidural infusion. Epidural boluses of 0.125% bupivacaine may be administered as guided clinically. A phenylephrine infusion can be used to maintain adequate blood pressure maintaining mean arterial pressures (MAP) above 60 mmHg. The epidural infusion can be paused if vasopressor requirements exceed 1 mcg/kg/min of phenylephrine or 0.1 mcg/kg/min of norepinephrine. The epidural infusion is to be paused if hemodynamics become unstable, either due to excessive blood loss or MAP consistently below 60 mmHg. The epidural infusion can be resumed when hemodynamics are stable.

The bupivacaine 0.125% epidural infusion is to be discontinued in the OR at the end of surgery and a standard epidural infusion of 0.1% bupivacaine at 4-6 ml/hr will be started in the PACU. The epidural infusion is followed up by an Acute Pain Service in the postoperative period that will titrate the infusion based on the patients' self-reported pain scores and MAP values.

Outcomes

Primary Outcomes

The primary study outcome is the postoperative consumption of opioids (measured in morphine or morphine-equivalents) in patients undergoing pancreatic resections in the control group compared with the study group. Each subject's morphine or morphine-equivalent consumption postoperatively will be assessed every 24 hours. All subjects will be assessed daily during their postoperative inpatient admission by a trained member of the Acute Pain Service who is blinded to the treatment arm of the study.

Secondary Outcomes

Secondary outcomes of the study include measures evaluated during the inpatient postoperative period as well during subsequent outpatient follow-up. Study team members blinded to the treatment group of the patient will assess all secondary outcomes. Patient recovery and healing postoperatively will be evaluated using various measures, such as visual analog scores (VAS), intravenous fluid requirements, anti-emetic doses, and return of bowel function. Serum inflammatory markers will be evaluated serially, preoperatively on day of surgery, three hours after the start of surgical incision in the operating room, on postoperative day 2, and at the initial postoperative visit 2-6 weeks after surgery. Postoperative delirium assessments will be performed when patients can be aroused sufficiently in order to be assessed for delirium (Richmond Agitation-Sedation Scale (RASS) > -4). Each patient will be assessed for delirium on postoperative day 2 as postoperative delirium typically first manifests 24-96 hours after surgery.

For non-verbal patients the CAM-ICU instrument will be used and for verbal patients, the 3D-CAM instrument will be used[40]. As delirium is a fluctuating disorder and can be missed with sporadic delirium assessments, a structured method of chart review will be used to complement the clinical assessments.
This combined approach (3D-CAM interview or CAM-ICU plus chart review) increases the sensitivity and retains specificity in detecting incident delirium. The trial staff has undergone formal training in clinical delirium assessment and on the chart review methodology.

Patients will be seen for their initial postoperative weeks at 2-6 weeks after hospital discharge and will undergo repeat PPSP evaluation at that time.

Patients will continue to be followed in clinic for 2 years postoperatively with laboratory and radiologic evaluation as deemed appropriate by the primary surgeon. Patients will be followed for tumor recurrence and overall survival. Data will be collected directly from subject's medical record; no study-specific procedures will be implemented at follow up visits.

Sample Size

Sample size estimation was performed based on the study primary outcome of postoperative opioid consumption. Based on our prior experience, this estimation will be based on the following assumptions[41]: Expected morphine consumption is 30 milligrams intraoperatively, 30 mg on postoperative day 1 (POD1), 20 mg on POD2 and 10 mg on POD3. Therefore, expected total morphine consumption in the first 72 hours is, on average, 80 mg. Then, assuming that the standard deviation of morphine consumption is 30 mg, that a 20 mg difference in morphine consumption between groups is a clinically meaningful reduction of opioid use and assuming normal distribution of morphine consumption in both patient groups, the proposed sample size for a = 0.05 and b = 0.2 would be 37 patients per group (74 patients in total). However, we propose to increase the sample size of the study to 150 total patients to account for patients lost to follow-up, inability to complete the scheduled pancreatic resection, data errors, and other un-anticipated study problems.

Recruitment

Participants will be recruited primarily through the Washington University Hepatobiliary-Pancreatic Surgery clinics. Subjects will be given verbal (initially) and then written descriptions of the study aims, procedures, risks, and benefits, and will be required to give written informed consent. A member of the investigative team provides all study descriptions, informed consent, and answers all questions. No deception is required for the purposes of this study. All subjects will be aware of the randomization used in this study to either the control or intervention group. Subjects are informed verbally and in writing that participation is voluntary and they may refuse to participate and may withdraw from the study at any time without penalty.

Allocation

Participants will be randomized in a 1:1 ratio into the control group with standard of care pain management regimen or the intervention group with the addition of epidural analgesia. Randomization will occur via randomized number generation.

This is a single-blind study. Patients and the primary investigative team will be aware of the randomization. However, all study members performing data collection will be blinded to the randomization.

Data Analysis and Management

Data analysis for this study will focus on the comparison of patient outcomes (postoperative morphine/morphine-equivalent consumption, measures of postoperative recovery, inflammatory markers, 3D-CAM/CAM-ICU assessments, QST) between the intervention and control study groups. Based on data distribution, continuous variables will be compared between the two groups using student's t test or the Mann Whitney U test as appropriate. When appropriate, significance of findings will be adjusted for multiple comparisons using the Bonferroni correction method.

The Center for Biomedical Informatics at Washington University will be used as the central location for data collection and management. Since 2008, Washington University has hosted Research Electronic Data Capture (REDCap), a secure, web-based application for building and storing online research and clinical trial databases. The REDCap servers are securely housed in an on-site limited access data center managed by the Center for Biomedical Informatics at Washington University. All web-based information transmission is encrypted and all data are stored on a private firewall protected network. All users are assigned individual user IDs and passwords and individual access is restricted on a role-specific basis. REDCap was developed specifically around HIPAA guidelines and is also implemented and maintained in accordance with institutional security guidelines.

Monitoring

The study team will monitor all study participants for adverse events. The principal investigator will report all unanticipated problems or adverse events, all conditions of noncompliance, and any new information that may affect the continued or current enrollment of study participants to the IRB. All events will be reported to the IRB within 10 working days of the event or of notification of the principal investigator of the event. The death of a study participant must be reported to the IRB within 1 working day of the event or of notification of the principal investigator of the event.

The specific monitoring plan for this investigation is commensurate with the risks and the size and complexity of the investigations planned. The potential risks are attributable to performing insertion of the epidural catheter and the use of bupivacaine for neuraxial analgesia. Based on these considerations, the monitoring plan involves engaging a colleague from the Department of Anesthesiology not involved in the study to serve in a monitoring capacity. Based on the small size and relatively low risks nature of the protocol, only a third person (the colleague), rather than a full Data Safety Monitoring Board will be used. The colleague will be an anesthesiologist knowledgeable in the risks associated with nerve blocks and local anesthetic administration. This individual will review the annual summary of adverse events. In addition, this colleague will review all reports of a Serious Adverse Event, or an Unexpected Adverse Event.

ETHICS AND DISSEMINATION

Ethics Approval and Consent

The E-PRO trial was provided ethical approval by the Washington University in St. Louis's Institutional Review Board which serves Washington University and Barnes-Jewish Hospital. Study recruitment and enrollment began in May 2016 and will continue through the end of 2017. Potential study participants will be given verbal and then written descriptions of the study aims, procedures, risks, and benefits, and written informed consent will be obtained for all participants. All participants are informed verbally and in writing that participation is voluntary and they may refuse to participate and may withdraw from the study at any time without penalty.

Confidentiality

Only the investigators and research team will have access to any protected health information of study participants and any study data. All subjects will be assigned a study ID number. All study data and samples will be coded with the assigned study ID number. A key to the code linking code numbers to patient names will be kept at a separate location, under lock and key; this link will be destroyed at the conclusion of this study. All data will be recorded by a member of the research team and will be stored in a password-protected electronic database stored on the departmental network drive. Study data will be not be entered into participants' medical records.

Dissemination

Dissemination plans include presentations at scientific conferences and scientific publications.

CONCLUSIONS

This trial investigates a wide spectrum of potential benefits to patients undergoing pancreatic resection. During the initial postoperative period, the use of epidural analgesia can aid in improving postoperative pain control, decreasing opioid consumption, reducing the incidence of delirium, and expediting recovery. In addition to improving immediate post-surgical pain control, epidural analgesia may reduce the development of persistent post-surgical pain, which can persist for weeks to years after surgery. Lastly, epidural analgesia can help reduce the body's stress response to a major operation, which has been linked to malignant progression and spread. Based on this trial, we seek to establish the role of epidural analgesia as part of the standard of care in future patients undergoing pancreatic operations.

Authors' Contributions

LMP and MMB are the primary authors of the E-PRO protocol. Their contributions include conceptualizing the study design, drafting and editing the protocol, and creating the electronic database REDCap used for data collection. WGH contributed to the E-PRO protocol by editing the protocol and recruiting patients for enrollment. SH contributed to the E-PRO protocol by conceptualizing the study design, drafting and editing the protocol, and supervising data

collection. LW contributed to the E-PRO protocol by editing the protocol, recruiting patients, and collecting data. MKu contributed to the E-PRO protocol by recruiting patients and collecting data. KF contributed to the E-PRO protocol and editing the protocol, creating the electronic database REDCap, coordinating patient enrollment and data collection. MKacontributed to the E-PRO protocol by conceptualizing the study design and editing the protocol. RAS contributed to the E-PRO protocol by conceptualizing the study design and editing the protocol. All authors including LMP, WGH, SH, LW, MKu, KF, MKa, RAS, and MMB have critically revised the E-PRO protocol and approved the final version. All authors agree to be accountable for the accuracy and integrity of all aspects of the E-PRO trial.

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Competing Interests Statement
None

FIGURE LEGEND

Figure 1. Study design.

SUPPLEMENTAL FILES

Supplemental 1. Quantitative sensory testing (QST) protocol.

References

[1] Park WY, Thompson JS, Lee KK. Effect of epidural anesthesia and analgesia on perioperative outcome: a randomized, controlled Veterans Affairs cooperative study. *Ann Surg*. 2001;234:560-571.

[2] Choi DX, Schoeniger LO. For patients undergoing pancreatoduodenectomy, epidural anesthesia and analgesia improves pain but increases rates of intensive care unit admission and alterations in analgesics. *Pancreas*. 2010;39(4):492-7.

[3] Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet*. 2006;367(9522):1618-25.

[4] Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. *Expert Rev Neurother*. 2009;9(5):723-44.

[5] Pogatzki-Zahn EM, Schnabel A, Zahn PK. Room for improvement: unmet needs in postoperative pain management. *Expert Rev Neurother*. 2012;12(5):587-600.

[6] Zhang JM, An J. Cytokines, inflammation, and pain. *Int Anesthesiol Clin*. 2007;45(2):27-37.

[7] DeVon HA, Piano MR, Rosenfeld AG, Hoppensteadt DA. The association of pain with protein inflammatory biomarkers: a review of the literature. *Nurs Res*. 2014;63(1):61-62.

[8] Uceyler N, Eberle T, Rolke R, Birklein F, Sommer C. Differential expression patterns of cytokines in complex regional pain syndrome. *Pain*. 2007;132(1-2):195-205.

[9] De Jongh RF, Vissers KC, Meert TF, Booij LH, De Deyne CS, Heylen RJ. The role of interleukin-6 in nociception and pain. *Anesth Analg*. 2003;96(4):1096-103.

[10] Woolf CJ, Costigan M. Transcriptional and posttranslational plasticity and the generation of inflammatory pain. *Proc Natl Acad Sci U S A*. 1999;96(4):7723-30.

[11] Burger V, D'Olimpio JT. Improving quality of life through pain control. *Clin J Oncol Nurs*. 2013;17(2):117-8.

[12] Chan C, Franssen B, Dominguez I, Ramirez-Del Val A, Uscanga LF, Compuzano M. Impact on quality of life after pancreatoduodenectomy: a prospective study comparing preoperative and postoperative scores. *J Gastrointest Surg*. 2012;16(7):1341-6.

[13] Carroll J, Alavi K. Pathogenesis and management of postoperative ileus. *Clin Colon Rectal Surg*. 2009;22(1):47-50.

[14] Leslie JB, Viscusi ER, Pergolizzi JV Jr, Panchal SJ. Anesthetic routines: the anesthesiologist's role in GI recovery and postoperative ileus. *Adv Prev Med*. 2011;2011: 976904. Epub 2010 Dec 29.

[15] Person B, Wexner SD. The management of postoperative ileus. *Curr Probl Surg*. 2006;43(1):6-65.

[16] Emick DM, Riall TS, Cameron JL, Winter JM, Lillemoe KD, Coleman J, Sauter PK, Yeo CJ. Hospital readmission after pancreaticoduodenectomy. *J Gastrointest Surg*. 2006;10(9):1243-52.

[17] Ahmad SA, Edwards MJ, Sutton JM, Grewal SS, Hansenman DJ, Maithel SK, Patel SH, Bentram DJ, Weber SM, Cho CS, Winslow ER, Scoggins CR, Martin RC, Kim HJ, Baker JJ, Merchant NB, Parikh AA, Kooby DA. Factors influencing readmission after pancreaticoduodenectomy: a multi-institutional study of 1302 patients. *Ann Surg*. 2012;256(3):529-37.

[18] Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008;454(7203):436-44.

[19] Marchesi F, Monti P, Leone BE, Zerbi A, Vecchi A, Piemonti L, Mantovani A, Allavena P. Increased survival, proliferation, and migration in metastatic human pancreatic tumor cells expressing functional CXCR4. *Cancer Res*. 2004;64(22): 8420-7.

[20] McKay CJ, Glen P, McMillan DC. Chronic inflammation and pancreatic cancer. *Best Pract Res Clin Gastroenterol*. 2008;22(1):65-73.

[21] Laird BJ, Scott AC, Colvin LA, McKeon AL, Murray GD, Fearon KC, Fallon MT. Cancer pain and its relationship to systemic inflammation: an exploratory study. *Pain*. 2011;152(2):460-3.

[22] Bar-Yosef S, Melamed R, Page GG, Shakhar G, Shakhar K, Ben-Eliyahu. Attenuation of the tumor-promoting effect of surgery by spinal blockade in rats. *Anesthesiology*. 2001;94:1066-73.

[23] Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. Their role in postoperative outcome. *Anesthesiology*. 1995;82(6):1474-506.

[24] Balcom JH 4th, Rattner DW, Warshaw AL, Chang Y, Fenandex-del Castillo C. Ten-year experience with 733 pancreatic resections: changing indications, older patients, and decreasing length of hospitalization. *Arch Surg*. 2001;136(4):391-8.

[25] Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, Hodgin MB, Sauter PK, Hruban RH, Riall TS, Schulick RD, Choti MA, Lillemoe KD, Yeo CJ. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. *J Gastrointest Surg*. 2006;10(6):1199-210.

[26] Matrisian L, Aizenberg R, Rosenzweig A. The alarming rise of pancreatic cancer deaths in the United States. http://www.pancan.org/section_research/reports/incidence_report.php. Accessed March 13, 2014.

[27] Cress RD, Yin D, Clarke L, Bold R, Holly EA. Survival among patients with adenocarcinoma of the pancreas: A population-based study (United States). *Cancer Causes Control*. 2006;17:403-9.

[28] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64(1):9-29.

[29] Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ. Cancer Statistics, 2006. *CA Cancer J Clin*. 2006;56:106-30.

[30] Hishinuma S, Ogata Y, Tamikawa M, Ozawa I, Hirabayashi K, Igarashi S. Patterns of recurrence after curative resection of pancreatic cancer, based on autopsy findings. *J Gastrointest Surg*. 2006;10(4):511-8.

[31] Gnerlich JL, Luka SR, Deshpande AD, Dubray BJ, Weir JS, Carpenter DH, Brunt EM, Strasberg SM, Hawkins WG, Linehan DC. Microscopic margins and patterns of treatment failure in resected pancreatic adenocarcinoma. *Arch Surg*. 2012;147(8):753-60.

[32] Sohal DP, Walsh RM, Ramanathan RK, Khorana AA. Pancreatic adenocarcinoma: treating a systemic disease with systemic therapy. *J Natl Cancer Inst*. 2014. Epub 2014 Feb 22.

[33] Scavonetto F, Yeoh TY, Umbreit EC, Weingarten TN, Gettman MT, Frank I, Boorjian SA, Karnes RJ, Schroeder DR, Rangel LJ, Hanson AC, Hofer RE, Sessler DI, Sprung J. Association between neuraxial analgesia, cancer progression, and mortality after radical prostatectomy: a large, retrospective matched cohort study. *Br J Anaesth.* 2013. Epub 2013 Dec 16.

[34] Holler JP, Ahibrandt J, Burkhardt E, Gruss M, Rohrig R, Knapheide J, Hecker A, Padberg W, Weigand MA. Peridural analgesia may affect long-term survival in patients with colorectal cancer after surgery (PACO-RAS-Study): an analysis of a cancer registry. *Ann Surg*. 2013;258(6):989-93.
[35] Christopherson R, James KE, Tableman M, Marshall P, Johnson FE. Long-term survival after colon cancer surgery: a variation associated with choice of anesthesia. *Anesth Analg*. 2008;107(1):325-32.
[36] Cummins KC 3rd, Xu F, Cummings LC, Cooper GS. A comparison of epidural analgesia and traditional pain management effects on survival and cancer recurrence after colectomy: a population-based study. *Anesthesiology*. 2012;116(4):797-806.
[37] Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, Brown DL, Heit JA, Mulroy MF, Rosenquist RW, Tryba M, Yuan CS. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med*. 2010;35:64-101.
[38] Finnerup NB, Sorenson L, Biering-Sorensen F, Johannesen IL, Jensen TS. Segmental hypersensitivity and spinothalamic function in spinal cord injury pain. *Ex Neurol*. 2007;207:139-149.
[39] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983 Jun;67(6):361-70.
[40] Ely, EW, Vanderbilt University. "Confusion Assessment Method for the ICU (CAM-ICU): The Complete Training Manual." Confusion Assessment Method for the ICU (CAM-ICU): The Complete Training Manual. March 1, 2014. Accessed December 14, 2016. http://www.icudelirium.org/docs/CAM_ICU_training.pdf.
[41] Mann C, Pouzeratte Y et al. Comparison of intravenous or epidural patient-controlled analgesia in the elderly after major abdominal surgery. *Anesthesiology*. 2000; 92:433-41.

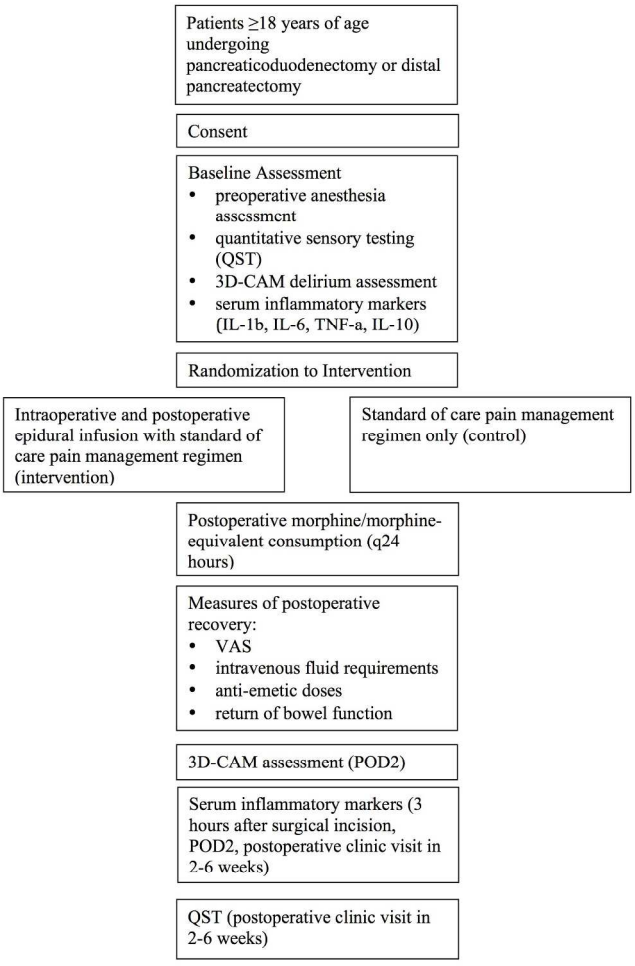

Figure 1. Study design

215x279mm (300 x 300 DPI)

Supplemental 1. Quantitative sensory testing (QST) protocol.

Quantitative sensory testing will be performed in the main assessment area on the abdomen, in close proximity to the surgical incision.

A description of the QST procedures follows:

Thermal detection and thermal pain thresholds
Equipment: The Thermal Sensory Analyzer (TSA-II or PATHWAY platform - Medoc, Ramat Yishai, Israel) will be used to determine thermal detection and pain thresholds. This equipment is used globally for functional assessment of pain and temperature-conducting nerve fibers (C and A-delta fibers).
Method and Background: Using the thermal sensory analyzer, cold and warm detection thresholds (CDT and WDT, respectively), as well as cold and heat pain thresholds (CPT and HPT, respectively) will be determined. The thermode with contact area of 9.0 cm^2 is applied to the tested site, and all thresholds are determined by continuous ramping of temperature from 32°C baseline temperature by 1°C/s until the subject presses the 'stop' button. Cut-off temperatures are 0°C and 50°C, to minimize thermal damage to the skin. The baseline temperature to which the thermode returns before each test is 32°C. The average threshold is calculated from three measurements in each area.

Determination of mechanical detection threshold (MDT)
Equipment: A set of standardised von Frey filaments (#1.65, #2.35, #2.44, #2.83, #3.22, #3.61, #3.84, #4.08, #4.17, #4.31, #4.74, #4.93, #5.07, #5.18, #5.46, #5.88, #6.10, #6.45, 6.65. The contact area of the filaments with the skin is of uniform size (<1 mm^2) and texture.

Methods and Background: Standardised von Frey filaments will be used in a modified "method of limits" manner using 3 series of increasing and decreasing stimulus intensities to determine the geometric average as the tactile detection threshold of the affected and unaffected skin areas.

Von Frey filaments of different stimulus intensities are used to determine the tactile detection thresholds. A #5.07 filament (eliciting 10 gram force)* is applied first, followed by filaments of consecutively lower intensity until the patient cannot detect the stimulus being applied. This respective force represents the first threshold value. The order in which the stimuli are applied is then reversed and stimuli of consecutively greater intensity are applied until sensation is detected (this intensity becomes the second value). Again filaments with decreasing intensity are applied until in total 3 upper and lower values of detection are fulfilled from which the mechanical detection threshold can be determined.

* In case the first von Frey filament (#5.07) is not detected, the next highest intensity filament which can be detected must be used as a starting intensity. However, the relevant force of this stimulus is not documented. Filaments with consecutively lower intensity are applied until the patient cannot detect the stimulus being applied. The procedure is followed as above; until in total 3 upper and lower values of detection are fulfilled from which the mechanical detection threshold can be determined.

Determination of mechanical pain thresholds (MPT)

Equipment: Same as for MDT determination.
Methods and Background:
Standardised von Frey filaments will be used in a modified "method of limits" manner using 3 series of increasing stimulus intensities to determine the average mechanical pain threshold of the affected and unaffected skin areas.
Beginning with an applied force of 8mN, stimuli increase in intensity until the sensation induced by increased pressure can be described as 'painful'. The corresponding force is used to represent the first MPT value. The procedure is then repeated a total of 3 times and until a total of 3 values are obtained, from which the mean mechanical pain threshold can be determined.

Determination of wind-up ratio (WUR)
Equipment: A pinprick stimulus with standardised intensity (#6.10 von Frey filament, approx. 98 gram) and a flat contact area of 0.25mm diameter.
Methods and Background: In this test a pinprick) is first applied singularly. After that a series of 10 identical pinprick stimuli are applied with a frequency of 1 s^{-1} within an area of 1 cm^2.
Immediately following the single stimulus and series of stimuli, an evaluation of the sensation must be provided according to NRS (0-10, '0': 'no pain', '10': 'worst pain imaginable'). A ratio is calculated using these values. This procedure shall be repeated twice. A geometric average of the 'wind-up' is calculated from the two ratios.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,2
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	1,2,9
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	1,9
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	9
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7,8

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	___3,4_____
	6b	Explanation for choice of comparators	___N/A_____
Objectives	7	Specific objectives or hypotheses	____6,7_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___4-6_____

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____7_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	___4,5_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____4-6_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_____6-8_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____8_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____6_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____6-7_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____4-5,11____

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____7_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____7_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____5_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____5-7_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____5_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____5-7_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____5-7_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____5-7_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____6-7_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____7-8_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____7-8_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____N/A_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____7,8_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____8_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	____N/A_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____8_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____8_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____8_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____8_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___4-5_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____N/A_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____9_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____10_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____8_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____8_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____9_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____9_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____9_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__Supplemental_
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____5,6_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.