IRB-HSR PROTOCOL

Investigator Agreement

BY SIGNING THIS DOCUMENT, THE INVESTIGATOR CONFIRMS:

1. I am not currently debarred by the US FDA from involvement in clinical research studies.
2. I am not involved in any regulatory or misconduct litigation or investigation by the FDA.
3. That if this study involves any funding or resources from an outside source, or if you will be sharing data outside of UVA prior to publication that you will contact the Dean's office regarding the need for a contract and letter of indemnification. If it is determined that either a contract or letter of indemnification is needed, subjects cannot be enrolled until these documents are complete.
4. The proposed research project will be conducted by me or under my close supervision. It will be conducted in accordance with the protocol submitted to and approved by the IRB including any modifications, amendments or addendums submitted and approved by the IRB throughout the life of the protocol.
5. That no personnel will be allowed to work on this protocol until they have completed the IRB-HSR On-line training and the IRB-HSR has been notified.
6. That all personnel working on this protocol will follow all IRB-HSR Policies and Procedures as stated on the IRB-HSR Website http://www.virginia.edu/vprgs/irb/ and on the School of Medicine Clinical Trials Office Website: http://knowledgelink.healthsystem.virginia.edu/intranet/hes/cto/sops/sop_index.cfm
7. I will ensure that all those delegated tasks relating to this study, whether explicitly or implicitly, are capable through expertise, training , experience or credentialing to undertake those tasks.
8. I confirm that the implications of the study have been discussed with all Departments that might be affected by it and have obtained their agreement for the study to take place.
9. That no subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment
10. That any materials used to recruit subjects will be approved by the IRB-HSR prior to use.
11. That all subjects will sign a copy of the most current consent form that has a non-expired IRB-HSR approval stamp.
12. That any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.
13. Any significant findings that become known in the course of the research that might affect the willingness of subjects to enroll or to continue to take part, will be promptly reported to the IRB.
14. I will report immediately to the IRB any unanticipated problems involving risk to subjects or to others including adverse reactions to biologics, drugs or medical devices.
15. That any serious deviation from the protocol will be reported promptly to the Board in writing.
16. That any data breach will be reported to the IRB, the UVa Corporate Compliance and Privacy Office , UVa Police as applicable.
17. That the continuation status report for this protocol will be completed and returned within the time limit stated on the form.
18. That the IRB-HSR office will be notified within 30 days of a change in the Principal Investigator or of the closure of this study.
19. That a new PI will be assigned if the current PI will not be at UVA for an extended period of time. If the current PI leaves UVa permanently, a new PI will be assigned PRIOR to the departure of the current PI.

20. All study team members will have access to the current protocol and other applicable documents such as the IRB-HSR Application, consent forms and Investigator Brochures.
21. Signed consent forms and other research records will be retained in a confidential manner. Records will be kept at least 6 years after completion of the study.
22. No data/specimens may be taken from UVa without a signed Material Transfer Agreement between OSP/SOM Grants and Contracts Office and the new institution. Original study files are considered institutional records and may not be transferred to another institution. I will notify my department administration regarding where the originals will be kept at UVa. The material transfer agreement will delineate what copies of data, health information and/or specimens may be taken outside of UVa. It will also approve which HIPAA identifiers may be taken outside of UVa with the health information or specimens.
23. If any member of study team leaves UVa, they are STRONGLY ENCOURAGED to use Exit Checklist found on IRB-HSR website at http://www.virginia.edu/provost/facultyexit.pdf.

The IRB reserves the right to terminate this study at any time if, in its opinion, (1) the risks of further experimentation are prohibitive, or (2) the above agreement is breached.

Investigators Experience

The principal investigator is an attending anesthesiologist with extensive experience in clinical research.

Signatures

Principal Investigator

_____	_____	_____
Principal Investigator Signature	Principal Investigator Name Printed	Date

The Principal Investigator signature is ONLY required if this is a new protocol, a 5 year update or a modification changing the Principal Investigator.

Department Chair

BY SIGNING THIS DOCUMENT THE DEPARTMENT CHAIR AGREES:

1. To work with the investigator and with the board as needed, to maintain compliance with this agreement.
2. That the Principal Investigator is qualified to perform this study.
3. That the protocol is scientifically relevant and sound.

_____	_____	_____
Department Chair or Designee Signature	Department Chair or Designee Name Printed	Date

The person signing as the Department Chair cannot be the Principal Investigator or a sub-investigator on this protocol.
The Department Chair or Designee signature is ONLY required if this is a new protocol or a modification changing the Principal Investigator.

Brief Summary/Abstract

We have chosen to study the reconstructive spinal surgery patient population because we believe that the use of alvimopan in these patients at the University of Virginia will give the scientific community significant insight into the broader applicability of this drug into other surgical populations, the impact of this drug on the perception of pain (as opposed to simply the consumption of opioids), and its impact on total hospital charges, resource utilization, and functional outcomes.

Background

Provide the scientific background, rationale and relevance of this project.

Pain control following major spine surgery is difficult to achieve. Opiates are often necessary in high doses, and may be associated with significant side effects. Such side effects may include urinary retention, altered mental status, depressed respiratory drive, and constipation, and may lead to reduced nutritional intake in the postoperative period. Importantly, post-operative nutrition may impact the incidence of complications following spine surgery.[1]

An emerging body of data suggests that intraoperative opiate use results in increased post-operative opiate requirements[2-4] although this is controversial.[5-7] Because of the side effects associated with opioid use, much effort has been devoted to the development of alternative and/or complementary analgesic regimens. Unfortunately, in early 2009 much of the promising data on alternative/complementary analgesic modalities was shown to have been fabricated. In all, twenty-one peer-reviewed papers in support of ketorolac, COX-2 inhibitors (celecoxib, rofecoxib, and valdecoxib), clonidine, verapamil, venlafaxine, pregabalin, and gabapentin were retracted. Thus, the goal of achieving improved perioperative pain control is as important, and distant, as ever

Alvimopan is a peripheral-acting opiate antagonist designed to decrease the gastrointestinal complications of perioperative systemic opioid administration. It has been studied in 11 randomized, controlled trials encompassing 4175 patients over the course of seven years. In all but one study, bowel recovery was improved following alvimopan administration, and in all but two, post-operative analgesia was reportedly unaffected

Despite existence of a large, growing body of literature supporting the use of alvimopan, further analysis is warranted for several reasons. First, and foremost, all eleven randomized trials of alvimopan were conducted using in patients undergoing intraabdominal surgery. While these patients universally suffer from post-operative ileus (because of proximity between the site of surgery to the GI tract), other patient populations (such as major spine surgery patients) also suffer from post-operative ileus

Second, the vast majority of data on alvimopan assesses effective analgesia by comparing morphine equivalents between groups (the implication being that if morphine equivalents are equal, no inhibition of analgesic effect has occurred). This methodology does not actually assess pain control or patient satisfaction

Third, several studies have shown an improvement in time to discharge or discharge order[8-12], without examining whether or not the difference in time to discharge translated into a reduction in hospital charges. Bell et al. pooled data from several alvimopan trials and estimated that mean hospital costs were reduced between $879 and $977 per patient, although this analysis was not based on the neurosurgical patient population.[8]

Lastly, the primary outcome in all eleven randomized, clinical trials is some variation of return of GI function. Patients who undergo reconstructive spinal procedures offer an additional clinical outcomes – functional status and postoperative satisfaction (as measured by the Owestry Disability Index [ODI], the short form 12, and the short form 36 scores)

Hypothesis to be Tested

Primary Objective: examine the impact of alvimopan on time to first bowel movement in patients who undergo major spinal surgery

Primary Hypothesis: the perioperative use of alvimopan in major spine surgery reduces the time to first bowel movement

Secondary Objective: examine the impact of alvimopan on:

- overall hospital cost
- quality of recovery
- pain scores

Secondary Hypotheses: the perioperative use of alvimopan in major spine surgery
1) reduces overall hospital cost [even when taking into account the cost of the drug]
2) results in earlier resumption of full PO intake and consequently improved post-operative nutrition

Study Design: Biomedical

1. Will controls be used? Yes

►**IF YES, explain the kind of controls to be used.** placebo controlled study

7. What is the study design?
Randomized, Double-Blind, Placebo-Controlled Trial

8. **Does the study involve a placebo?**Yes

►**IF YES, provide a justification for the use of a placebo**
Compelling methodological reasons for use of placebo;
Participants are not deprived of interventions they would otherwise receive; *and*
Research intended to develop interventions that will benefit the host population.

Human Participants

1. How many subjects will sign a consent form under this UVa protocol? **60**

2. Provide an estimated time line for the study.100% enrolled in 2 years

Inclusion/Exclusion Criteria

INSTRUCTIONS:
The inclusion and exclusion criteria should be written in bullet format.

If this is a collection of only retrospective* specimens or data, the inclusion criteria must include a start and stop date for when specimens/ data will be collected.
The stop date must be prior to the version date of this protocol.
*Retrospective: all specimens are in a lab at the time this protocol is approved by the IRB. All data exists in medical records or records from previous studies at the time this protocol is approved by the IRB.

1. List the criteria for inclusion

1. Major spine surgery scheduled as part of clinical care
2. 18-80 years

2. List the criteria for exclusion

1. More than three doses of any opioid within one week of surgery
2. Pregnancy-
3. Prisoners
4. Unable to provide consent
5. Emergency surgery
6. Chronic kidney disease stage 5 (GFR < 15 ml/min)
7. Severe hepatic impairment
8. Recent myocardial infarction (within the last 3 months)
9. Allergy to any study related medications
10. Participation in another interventional study during the study period

3. List any restrictions on use of other drugs or treatments.
None

Statistical Considerations

a. **Is stratification/randomization involved?** Yes

►**IF YES, describe the stratification/ randomization scheme.**

- randomization will occur to either the alvimopan or placebo group after confirmation of eligibility on the day of surgery
- the randomization will be performed and the blind maintained by the Investigational Pharmacy

►**IF YES, who will generate the randomization scheme?**

__x___ UVa Investigational Drug Service (IDS)

2. What are the statistical considerations for the protocol?
For the purpose of the final analysis, the official clinical database will not be unblinded until medical/scientific review has been completed at the end of the entire study, protocol violators have been identified (if appropriate), and data has been declared complete.

Siny Tsang, PhD will perform the analysis for UVA

Abdel Malek,Amir L. will extract data from CDR. Abdel works for the Department of Anesthesiology and extracts data as part of his routine job duties

Statistical Methods: For continuous variables, normality will be assessed using the Kolmogorov-Smirnov test. The Mann-Whitney U-test will be used to compare non-normally distributed data, and normally distributed data will be assessed by the Student t-test for equality of means. Categorical data will be analyzed using χ^2 or Fisher's exact test,if the count is < 5 in any cell. .

1. Time to event data (time to first bowel movement) will be analyzed using the rank-sum test.

2.visual analog scale , overall hospital charges , time to resumption of PO intake ,functional outcomes QR-40 will be analyzed in the following ways:

- 11-point Numeric rating scale and QR-40 will be analyzed by way of a mixed model for repeated measures (MMRM).
- For hospital charges, either a t-test or Wilcoxon rank sum test (depending on the assessment of normality, as noted above).
- For time to resumption of PO intake we will assume no censoring and will use the rank sum test. Finally pain scores will be calculated and displayed using summary statistics empirically without comparison testing.

All tests will be 2-sided and we will consider a P value **<**0.05 to be statistically significant.

3. Provide a justification for the sample size used in this protocol.

In order to power this study, we evaluated the mean time to first bowel movement at our institution, which was 3.27 days (σ = 1.10)

Based on published data 519 women undergoing gynecological surgery, we predict that perioperative alvimopan will reduce the time to first bowel movement by 30%.[13] Assuming that the placebo group will require 3.27 days to achieve a bowel movement, that alvimopan reduces time to first bowel movement by 30% (0.98 days) without changing the standard deviation (σ = 1.10), and setting α to 0.05, power analysis suggests that we will need to randomize 42 patients in order to have a 80% chance of not making a type II error. To factor for a 10-15% dropout rate, we would recruit 60 subjects for this study.

4. What is your plan for primary variable analysis?

Time to event data (time to first bowel movement) will be analyzed using the rank-sum test.

5. What is your plan for secondary variable analysis?

visual analog scale ,overall hospital charges , time to resumption of PO intake , functional outcomes QR40 8) will be analyzed in the following ways:

- 11-point Numeric rating scale and will be analyzed by way of a mixed model for repeated measures (MMRM).
- For hospital charges, either a t-test or Wilcoxon rank sum test (depending on the assessment of normality, as noted above).
- For time to resumption of PO intake we will assume no censoring and will use the rank sum test. Finally pain scores will be calculated and displayed using summary statistics empirically without comparison testing.

6. Have you been working with a statistician in designing this protocol? Yes

Siny Tsang, PhD

7. Will data from multiple sites be combined during analysis? No

Biomedical Research

1. List the procedures, in bullet form, that will be done for RESEARCH PURPOSES as stipulated in this protocol.

- Subjects will be consented
- Prior to study randomization, subjects will undergo a physical exam and review of medical history
- All women of child bearing potential will have a urine pregnancy test performed prior to administration of study drug pre-operatively
- Subjects will be randomized to either the alvimopan or placebo group
- Alvimopan or placebo administered orally pre-operatively
- Alvimopan or placebo administered orally or per NG twice daily post-operatively for up to seven days post-operatively, or until the time of discharge, whichever occurs first, to a maximum of 15 doses
- All intraoperative data recorded on the anesthesia record will be collected prospectively.
- BIS scores, when available, will be collected at the completion of surgery.
- Neuromonitoring data (ex. latency, amplitude, significant signal changes) will be collected at the completion of surgery.
- Postoperatively, visual analog scale (VAS) scores will be assessed daily at morning rounds.
- Additionally, nutritional intake and in hospital complications will be recorded, as will the patient's report of pain (on the 0-10 pain scale), time to first solid intake, time to first flatus and bowel movement (**primary outcome**), time to first ambulation, and consumption of all pain medications (intravenous and by mouth).
- ICU stay and hospital stay will be noted Initial post-op pain management orders will be entered by the Anesthesiologist
- to standardize opioid requirements, patients will initially be ordered hydromorphone as the intravenous opioid of choice (PCA and prn), and will only be changed (fentanyl) if specifically requested by the primary service.
- Patients will also be ordered oxycodone as the initial PO opioid of choice, and only changed to other medications (hydrocodone) if specifically requested by the primary service
- At the completion of hospitalization, QR40 will be used to assess the patients' pain and quality of life at discharge.

  Total patient charges will be extracted from the University of Virginia's Clinical Data Repository.

2. Will you be using data/specimens in this study that were collected previously, with the use of a research consent form, from another research study? No

3. Will any of the procedures listed in item # 1 have the potential to identify an incidental finding? This includes ALL procedures, assessments and evaluations that are being done for RESEARCH PURPOSES that may or may not be considered investigational. No

4. Do any of the procedures listed above, under question # 1, utilize any imaging procedures for RESEARCH PURPOSES?No

5. Will you be using viable embryos? No

6. Will you be using embryonic stem cells? No

9. **Are any aspects of the study kept secret from the participants?** Yes

►**IF YES, describe:** the randomized study drug/ placebo is blinded

10. **Is any deception used in the study?** No

9. Will your study involve measures (C-SSRS/BID/SCID etc.) used to assess for depression and/or suicidality for research purposes? No

APPENDIX: Clinical Data Repository

1. Will you be obtaining data from the UVa Clinical Data Repository (CDR)? yes

CATEGORY	DATA ELEMENTS	CHECK ALL THAT APPLY
Demographics	e.g. Gender, race, age	
Administrative	e.g. Includes payor, payscale, length of stay, fact of visits (inpatient or outpatient), locations of service (inpatient or outpatient), providers	
Financial	e.g. Charges or costs associated with care	x
Clinical Data	e.g. Diagnoses	
	e.g. Procedures	
	e.g. Mortality	
	e.g. Laboratory / Microbiology Results	
	e.g. Medications	
	e.g. Vitals, Height / Weight, Other Clinical Parameters	
	e.g. Other (specify)	
Narrative Reports	e.g. Includes discharge summaries, pathology reports, operative notes, etc.	
Other	Explain:	

Data and Safety Monitoring Plan

INSTRUCTIONS:
If you have any questions completing this section call 243-9847 for assistance.
A Sponsor is defined as entity that will receive data prior to publication.

1. Definition:

1.1 How will you define <u>adverse events</u> (AE)) for this study?

__x___An adverse event will be considered any undesirable sign, symptom or medical or psychological condition **only if the event is considered to be related** to the investigational drug/device/intervention. Medical condition/diseases present before starting the investigational drug/intervention will be considered adverse events only if they worsen after starting study treatment/intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research. Adverse events also include any problems associated with the use of an investigational device that adversely affects the rights, safety or welfare of subject s.

1.2 How will you define <u>serious adverse events</u>?

__x___A serious adverse event will be considered any undesirable sign, symptom, or medical condition which is fatal, is life-threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability/incapacity, constitutes a congenital anomaly or birth defect, is medically significant and which the investigator regards as serious based on appropriate medical judgment. An important medical event is any AE that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions of SAEs.

1.3 What is the definition of an <u>unanticipated problem?</u>

Do not change this answer

An unanticipated problem is any event, experience that meets ALL 3 criteria below:

- Is unexpected in terms of nature, severity or frequency given the research procedures that are described in the protocol-related documents AND in the characteristics of the subject population being studies
- Related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures involved in the research study.
- The incident suggests that the research placed the subject or others at greater risk of harm than was previously known or recognized OR results in actual harm to the subject or others

○ **What are the definitions of a protocol violation and/or noncompliance?**

Do not change this answer

A **protocol violation** is defined as any change, deviation, or departure from the study design or procedures of research project that is NOT approved by the IRB-HSR prior to its initiation or implementation. Protocol violations may be major or minor violations.

Noncompliance can be a protocol violation OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulation**s**. Noncompliance may be serious or continuing.

Additional Information: see the IRB-HSR website at http://www.virginia.edu/vpr/irb/HSR_docs/Forms/Protocol_Violations_%20Enrollment_Exceptions_Instructions.doc

- **If pregnancy occurs how will this information be managed?**

__x___ Unanticipated Problems- will follow Unanticipated Problem recording and reporting procedures outlined in section 3.

- **What is the definition of a Protocol Enrollment Exception?**

____Protocol has a sponsor or a Data & Safety Monitoring Board (DSMB) outside of UVa. An enrollment exception is the DSMB or sponsor's prospective approval for the enrollment of a research subject that fails to meet current IRB-HSR approved protocol inclusion criteria, or falls under protocol exclusion criteria. Enrollment exceptions only apply to a single individual. Such a request should be rare and justified in terms of serving the best interests of the potential study participant.

- **What is the definition of a data breach?**

Do not change this answer

A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

Additional Information may be found on the IRB-HSR Website: Data Breach

2. Identified risks and plans to minimize risk

2.1 What risks are expected due to the intervention in this protocol?

Expected Risks related to study participation.	Frequency
• Constipation	Occurs frequently
• Flatulence (gas)	Occurs frequently

• Dyspepsia (upset stomach)	Occurs frequently
• Anemia (low blood count	Occurs infrequently
• Urinary retention	Occurs infrequently
• Back pain	Occurs infrequently
Hypokalemia (low potassium	Occurs infrequently
Reproductive Risks Specify potential reproductive risks here	Minimized due to the requirements of this protocol.
Violation of subject's privacy and confidentiality	Minimized due to the requirements of the privacy plan in this protocol

The drug has shown an increase in heart attack when used long term, but no evidence of this has been seen with short-term use.

2.2 List by bullet format a summary of safety tests/procedures/observations to be performed that will minimize risks to participants:

- adequate screening
- AE monitoring at each visit

2.3 Under what criteria would an INDIVIDUAL SUBJECT'S study treatment or study participation be stopped or modified

___x__At subject, PI or sponsor's request

_x____Treatment would be stopped if the subject had a serious adverse event deemed related to study,

- **Under what criteria would THE ENTIRE STUDY need to be stopped.**

__x___Per IRB, PI,

2.5 What are the criteria for breaking the blind/mask?

___x__Other: the purpose of the final analysis, the official clinical database will not be unblinded until medical/scientific review has been completed at the end of the entire study, protocol violators have been identified (if appropriate), and data has been declared complete.

How will subject withdrawals/dropouts be reported to the IRB prior to study completion?

__x___IRB-HSR continuation status form

3. Adverse Event / Unanticipated Problem Recording and Reporting

3.1 Will all adverse events, as defined in section 1.1, be collected/recorded? No

►IF NO, what criteria will be used?

x_____Only adverse events that are deemed related AND serious

3.2 How will adverse event data be collected/recorded? Check all that apply

__x___Paper AE forms/source documents

3.3. How will AEs be classified/graded? Check all that apply

__x___Mild/Moderate/Severe

_X_ Serious/Not serious Required for all protocols

- **What scale will the PI use when evaluating the relatedness of adverse events to the study participation?**

__x___The PI will determine the relationship of adverse events to the study using the following scale:

Related:	AE is clearly related to the intervention
Possibly related:	AE may be related to the intervention
Unrelated:	AE is clearly not related to intervention

3.5 When will recording/reporting of adverse events/unanticipated problems begin?

___x__After subject begins study drug/ device placement/intervention /study-related procedure/specimen collection

3.6 When will the recording/reporting of adverse events/unanticipated problems end?

___x__ End of study drug/device/intervention/participation

3.7 How will Adverse Events, Unanticipated Problems, Protocol Violations and Data Breaches be reported? Complete the table below to answer this question

Type of Event	**To whom will it be reported:**	*Time Frame for Reporting*	*How reported?*
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation *An internal event is one that occurs in a subject enrolled in a UVa protocol*	IRB-HSR	Within 24 hours	IRB Online and phone call www.irb.virginia.edu/

Internal, Serious, related, Unexpected adverse event	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event. *Timeline includes submission of signed hardcopy of AE form.*	IRB Online www.irb.virginia.edu/
Unanticipated Problems that are not adverse events or protocol violations This would include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. *http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Reporting_Requirements-Unanticipated_Problems.doc)*
Protocol Violations/Noncompliance *The IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by your sponsor, if applicable.* **OR** **Enrollment Exceptions** *See definition- only allowed if there is a commercial sponsor or a DSMB that has granted the enrollment exception.*	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Violation, Noncompliance and Enrollment Exception Reporting Form *http://www.virginia.edu/vprgs/irb/hsr_forms.html* *Go to 3rd bullet from the bottom.*
Data Breach	The UVa Corporate Compliance and Privacy Office ITC: if breach involves electronic data Police if breach includes items that are stolen: Stolen on UVA Grounds	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 **ITC:** Information Security Incident Reporting procedure, http://www.itc.virginia.edu/security/reporting.html UVa Police-Phone- (434) 924-7166

	OR Stolen off UVa Grounds- contact police department of jurisdiction of last known location of PHI		

4. How will the endpoint data be collected/recorded. Check all that apply

__x___Protocol specific case report forms

__x___Source documents

___x__Database: to be stored on the "O" drive

5. Data and Safety Oversight Responsibility

5.1. Who is responsible for overseeing safety data for this study?

INSTRUCTIONS:
e.g. Who is looking at data in aggregate form to identify trends?
Check all that apply

___x__No additional oversight body other than PI at UVa Skip question 5.2

5.2. What is the composition of the reviewing body and how is it affiliated with the sponsor? *n/a*

5.3. What items will be included in the aggregate review conducted by the PI?

___x__All adverse events

___x__Unanticipated Problems

__x___Protocol violations/Issues of noncompliance

___x__Audit results

_____Application of dose finding escalation/de-escalation rules

These should be outlined under 2.4.

__x___Application of study designed stopping/decision rules

___x__Early withdrawals

___x__Whether the study accrual pattern warrants continuation/action

___x__Endpoint data

a. How often will aggregate review occur?

For additional information on aggregate review see:
www.virginia.edu/vpr/irb/hsr/continuations.html#aggreview

__x___Annually

5.5. How often will a report, regarding the outcome of the review by the DSMB/DSMC, be sent to the UVa PI? n/a

5.6. How will a report of the information discussed in question 5.4 OR 5.5 be submitted to the IRB?

__x___Part of IRB-HSR continuation status form

Risk/ Benefit Analysis

1. What are the potential benefits for the participant as well as benefits which may accrue to society in general, as a result of this study?

Opiates are often necessary in high doses, and may be associated with significant side effects. Such side effects may include urinary retention, altered mental status, depressed respiratory drive, and constipation, and may lead to reduced nutritional intake in the postoperative period. The potential benefit for the participant may be the reduction of these side effects.

We have chosen to study the reconstructive spinal surgery patient population because we believe that the use of alvimopan in these patients at the University of Virginia will give the scientific community significant insight into the broader applicability of this drug into other surgical populations, the impact of this drug on the perception of pain (as opposed to simply the consumption of opioids), and its impact on total hospital charges, resource utilization, and functional outcomes

2. Do the anticipated benefits justify asking subjects to undertake the risks?

The risks are those of opioids and the risks of the study drug. The benefit may improve bowel outcomes thus the risk benefit ratio is favorable.

Bibliography

1. Stambough JL, Beringer D. Postoperative wound infections complicating adult spine surgery. Journal of spinal disorders 1992;5:277-85.
2. Crawford MW, Hickey C, Zaarour C, Howard A, Naser B. Development of acute opioid tolerance during infusion of remifentanil for pediatric scoliosis surgery. Anesthesia and analgesia 2006;102:1662-7.
3. Guignard B, Bossard AE, Coste C, et al. Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. Anesthesiology 2000;93:409-17.
4. Rauf K, Vohra A, Fernandez-Jimenez P, O'Keeffe N, Forrest M. Remifentanil infusion in association with fentanyl-propofol anaesthesia in patients undergoing cardiac surgery: effects on morphine requirement and postoperative analgesia. British journal of anaesthesia 2005;95:611-5.
5. Cortinez LI, Brandes V, Munoz HR, Guerrero ME, Mur M. No clinical evidence of acute opioid tolerance after remifentanil-based anaesthesia. British journal of anaesthesia 2001;87:866-9.
6. Fletcher D, Pinaud M, Scherpereel P, Clyti N, Chauvin M. The efficacy of intravenous 0.15 versus 0.25 mg/kg intraoperative morphine for immediate postoperative analgesia after remifentanil-based anesthesia for major surgery. Anesthesia and analgesia 2000;90:666-71.
7. Lee LH, Irwin MG, Lui SK. Intraoperative remifentanil infusion does not increase postoperative opioid consumption compared with 70% nitrous oxide. Anesthesiology 2005;102:398-402.
8. Bell TJ, Poston SA, Kraft MD, Senagore AJ, Delaney CP, Techner L. Economic analysis of alvimopan in North American Phase III efficacy trials. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists 2009;66:1362-8.
9. Delaney CP, Weese JL, Hyman NH, et al. Phase III trial of alvimopan, a novel, peripherally acting, mu opioid antagonist, for postoperative ileus after major abdominal surgery. Diseases of the colon and rectum 2005;48:1114-25; discussion 25-6; author reply 27-9.

10. Ludwig K, Enker WE, Delaney CP, et al. Gastrointestinal tract recovery in patients undergoing bowel resection: results of a randomized trial of alvimopan and placebo with a standardized accelerated postoperative care pathway. Archives of surgery 2008;143:1098-105.
11. Viscusi ER, Goldstein S, Witkowski T, et al. Alvimopan, a peripherally acting mu-opioid receptor antagonist, compared with placebo in postoperative ileus after major abdominal surgery: results of a randomized, double-blind, controlled study. Surgical endoscopy 2006;20:64-70.
12. Wolff BG, Michelassi F, Gerkin TM, et al. Alvimopan, a novel, peripherally acting mu opioid antagonist: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial of major abdominal surgery and postoperative ileus. Annals of surgery 2004;240:728-34; discussion 34-5.
13. Herzog TJ, Coleman RL, Guerrieri JP, Jr., et al. A double-blind, randomized, placebo-controlled phase III study of the safety of alvimopan in patients who undergo simple total abdominal hysterectomy. American journal of obstetrics and gynecology 2006;195:445-53.

APPENDIX: Legal/Regulatory

Recruitment

The following procedures will be followed:

- Finders fees will not be paid to an individual as they are not allowed by UVa Policy.
- All recruitment materials will be approved by the IRB-HSR prior to use. They will be submitted to the IRB after the IRB-HSR has assigned an IRB-HSR # to the protocol.
- Only those individuals listed as personnel on this protocol will recruit and or conduct the consenting process with potential subjects.

Retention Incentives

Any item used by the sponsor/ study team to provide incentive to a subject to remain in the study, other than compensation identified in the Payment section, will be submitted to the IRB for review prior to use. The IRB-HSR will provide the study team with a Receipt Acknowledgement for their records. Retention incentive items are such things as water bottles, small tote bags, birthday cards etc. Cash and gift cards are not allowed as retention incentives.

Clinical Privileges

The following procedures will be followed:

- Investigators who are members of the clinical staff at the University of Virginia Medical Center must have the appropriate credentials and been granted clinical privileges to perform specific clinical procedures whether those procedures are experimental or standard.
- The IRB cannot grant clinical privileges.
- Performing procedures which are outside the scope of the clinical privileges that have been granted may result in denial of insurance coverage should claims of negligence or malpractice arise.
- Personnel on this protocol will have the appropriate credentials and clinical privileges in place before performing any procedures required by this protocol.
- Contact the Clinical Staff Office- 924-9055 or 924-8778 for further information.

Sharing of Data/Specimens

Data and specimens collected under an IRB approved protocol are the property of the University of Virginia. You must have “permission” to share data/ specimens outside of UVa other than for a grant application and or

publication. This "permission" may come in the form of a contract with the sponsor or a material transfer agreement (MTA) with others. A contract/ MTA is needed to share the data outside of UVa even if the data includes no HIPAA identifiers and no code that could link the data back to a HIPAA identifier.

- No data will be shared outside of UVa, beyond using data for a grant application and or publication, without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.
- No specimens will be shared outside of UVa without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.

Prisoners

If the original protocol/ IRB application stated that no prisoners would be enrolled in this study and subsequently a subject becomes a prisoner, the study team must notify the IRB immediately. The study team and IRB will need to determine if the subject will remain in the study. If the subject will remain in the study, the protocol will have to be re-reviewed with the input of a prisoner advocate. The prisoner advocate will also have to be involved in the review of future continuations, modifications or any other reporting such as protocol violations or adverse events.

Prisoner- Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.
For additional information see the OHRP website at http://www.hhs.gov/ohrp/policy/populations/index.html

Compensation in Case of Injury

If a subject requests compensation for an injury, the study team should notify the IRB-HSR (924-9634/2439847) the UVa Health System Patient Relations Department (924-8315). As a proactive courtesy, the study team may also notify UVa Health System Patient Safety and Risk Management (924-5595).

On request, the study team should provide the Risk Management Office with the following information/documents:

- Subject Name and Medical Record Number
- Research medical records
- Research consent form
- Adverse event report to IRB
- Any letter from IRB to OHRP

Subject Complaints

During a research study, the study team may receive complaints from a subject. If the study team is uncertain how to respond to a complaint, or is unable to resolve it with the subject, the study team may contact the IRB-HSR (924-9634/243-9847), the UVa Health System Patient Relations Department (924-8315).

Request for Research Records from Search Warrant or Subpoena

If the study team receives a request for research records from a search warrant or subpoena, they should notify UVa Health Information Services at 924-5136. It is important to notify them if information from the study is protected by a Certificate of Confidentiality.

APPENDIX: Non- UVa Personnel

1. **Explain the duties of non-UVA personnel on this protocol.**
Answer/Response: Only Statistical analysis will be performed by the non-UVA personnel.

2. **Explain your plans for training and oversight of these personnel**.
Answer/Response: The statistician is a PhD that we have worked with previously here at UVA, before she moved to Columbia University. She has previously done the UVA CITI training . No additional training will be required. Oversight will be conducted by phone and email contact.

3. **How do you plan to access any study records the non-UVA personnel might maintain?**
Answer/Response: It will not be necessary for us to access the de-identified data that the statistician will maintain.

4. **Will the non- UVA personnel be exposed to any additional risk while working on this protocol?**
Answer/Response: No

►**IF YES, what training, precautions will be taken to protect them?**
Answer/Response:

5. **List name of any other institution with which they have an affiliation**.
Answer/Response: Columbia University

6. **Will the non- UVa personnel have access to UVa patients or their health information along with any HIPAA identifiers prior to consent?** No
Answer/Response: **Non- UVa personnel will not have access to UVa patients or their health information along with any HIPAA identifiers prior to consent.**

►IF YES, check the HIPAA identifiers below they will have access to:

YES	NO	
	x	1. Name
	x	2. All geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of the zip code if, according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same 3 initial digits contains more than 20,000 people and (2) The initial 3 digits of a zip code for all such geographic units containing 20,000 is changed to 000.

	x	3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older. *[This means you may record the year but not record the month or day of any date related to the subject if the subject is under the age of 89. In addition if the subject is over the age of 89 you may not record their age and you may not record the month, day or year of any date related to the subject]*
	x	4. Telephone numbers
	x	5. Fax numbers
	x	6. Electronic mail addresses
	x	7. Social Security number
	x	8. Medical Record number
	x	9. Health plan beneficiary numbers
	x	10. Account numbers
	x	11. Certificate/license numbers
	x	12. Vehicle identifiers and serial numbers, including license plate numbers
	x	13. Device identifiers and serial numbers
	x	14. Web Universal Resource Locators (URLs)
	x	15. Internet Protocol (IP) address numbers
	x	16. Biometric identifiers, including finger and voice prints
	x	17. Full face photographic images and any comparable images
	x	18. Any other unique identifying number, characteristic, code that is derived from or related to information about the individual (e.g. initials, last 4 digits of Social Security #, mother's maiden name, first 3 letters of last name.)
	x	19. Any other information that could be used alone or in combination with other information to identify an individual. (*e.g. rare disease, study team or company has access to the health information and a HIPAA identifier or the key to the code* .)

7. If any items above are checked YES, list names of non- UVa affiliated individuals who will have access.
NA

8. Has the individual listed above obtained approval from the School of Medicine via the SOM Volunteer in Research Form?

Answer/Response: The statistician will be contracted to perform the analysis. She will not be a volunteer.

NOTE:

- If any item other than 2 or 3 is checked in the Table under Question # 6 and the individual listed under # 7 has NOT obtained approval from the School of Medicine via the SOM Volunteer in Research Form, tracking of the disclosure by the study team will be required via EPIC.

- If only item 2 or 3 is noted and the individual has NOT obtained approval from the School of Medicine via the SOM Volunteer in Research Form, a HIPAA Data Use Agreement will be required in a contract/ agreement between the unaffiliated investigator and UVa.

APPENDIX: Non- UVa Personnel

2. **Explain the duties of non-UVA personnel on this protocol.**
   Answer/Response: Merck, the sponsor, will review the article with results pre-publication.
2. **Explain your plans for training and oversight of these personnel**.
   Answer/Response: No training or oversight will be need for the sponsor Merck.
3. **How do you plan to access any study records the non-UVA personnel might maintain?**
   Answer/Response: We will not access study records **the non-UVA personnel might maintain. De-identified data will be secure emailed to the ststistician. Once analysis is done the results will be returned to UVA in the same manner.**
4. **Will the non- UVA personnel be exposed to any additional risk while working on this protocol?**
   Answer/Response: No
   ►**IF YES, what training, precautions will be taken to protect them?**
   Answer/Response:

5. **List name of any other institution with which they have an affiliation**.
   Answer/Response: Merck

6. **Will the non- UVa personnel have access to UVa patients or their health information along with any HIPAA identifiers prior to consent?** No
Answer/Response: **Non- UVa personnel will not have access to UVa patients or their health information along with any HIPAA identifiers prior to consent.**

►IF YES, check the HIPAA identifiers below they will have access to:

YES	NO	
	x	1. Name
	x	2. All geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of the zip code if, according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same 3 initial digits contains more than 20,000 people and (2) The initial 3 digits of a zip code for all such geographic units containing 20,000 is changed to 000.
	x	3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.

		[This means you may record the year but not record the month or day of any date related to the subject if the subject is under the age of 89. In addition if the subject is over the age of 89 you may not record their age and you may not record the month, day or year of any date related to the subject]
	x	4. Telephone numbers
	x	5. Fax numbers
	x	6. Electronic mail addresses
	x	7. Social Security number
	x	8. Medical Record number
	x	9. Health plan beneficiary numbers
	x	10. Account numbers
	x	11. Certificate/license numbers
	x	12. Vehicle identifiers and serial numbers, including license plate numbers
	x	13. Device identifiers and serial numbers
	x	14. Web Universal Resource Locators (URLs)
	x	15. Internet Protocol (IP) address numbers
	x	16. Biometric identifiers, including finger and voice prints
	x	17. Full face photographic images and any comparable images
	x	20. Any other unique identifying number, characteristic, code that is derived from or related to information about the individual (e.g. initials, last 4 digits of Social Security #, mother's maiden name, first 3 letters of last name.)
	x	21. Any other information that could be used alone or in combination with other information to identify an individual. (*e.g. rare disease, study team or company has access to the health information and a HIPAA identifier or the key to the code* .)

7. If any items above are checked YES, list names of non- UVa affiliated individuals who will have access.
NA

8. Has the individual listed above obtained approval from the School of Medicine via the SOM Volunteer in Research Form?

Answer/Response: Merck is a sponsor of this study.

NOTE:

- If any item other than 2 or 3 is checked in the Table under Question # 6 and the individual listed under # 7 has NOT obtained approval from the School of Medicine via the SOM Volunteer in Research Form, tracking of the disclosure by the study team will be required via EPIC.
- If only item 2 or 3 is noted and the individual has NOT obtained approval from the School of Medicine via the SOM Volunteer in Research Form, a HIPAA Data Use Agreement will be required in a contract/ agreement between the unaffiliated investigator and UVa.

APPENDIX: Drug Information

1. What is the name of the approved drug, device or biologic?
Alvimopan

2. What document have you provided to confirm FDA approval?
Package insert

3. Is the study required by the FDA? No

4. Is the study initiated by an investigator and not a commercial company? Yes

5. Is the study retrospective? No

6. Does the study involve research on a drug/ device in an already approved population/ condition? Yes

7. Does the study involve research only on a drug and NOT on a device? Yes

APPENDIX: Pharmacy-Approved Drug

8. What is the name of the drug?
Alvimopan

9. What dose will be utilized in this study?
The placebo group will receive a placebo pill, by mouth, on the day of (but prior to the start of) surgery. The treatment group will receive 12 mg of alvimopan, by mouth, on the day of (but prior to the start of) surgery. The placebo group will receive the placebo twice per day (either by mouth or by NG tube), and the treatment group will receive 12 mg alvimopan twice a day (either by mouth or by NG tube) for up to seven days post-operatively, or until the time of discharge, whichever occurs first, to a maximum of 15 doses.

10. What will be the frequency of dosing in this study?
BID up to 15 doses

11. What will be the duration of dosing in this study?
BID up to seven days post-operatively, or until the time of discharge, whichever occurs first, to a maximum of 15 doses.

12. What route of administration will be utilized? PO or NG

13. Will drug need to be prepared by the UVa Investigational Drug Service (IDS)?
__x___ NO- Drug will be prepared and/or administered per package insert

14. Are there any special handling instructions mandated by the study (e.g. weighing hazardous materials)?

No

15. Does the protocol provide provisions for dose titration, dose reductions, and or re-challenged (if drug is stopped), etc.? NO

16. How will missed doses be handled?
missed doses will be documented in the medical record and CRF

17. Will a comparator (active or placebo) be utilized in the protocol? Yes
►IF YES, comparator is:

___x__ Placebo*:* Provided by Merck

18. Does this study involve research on a drug, biologic, supplement or food additive? Yes

►IF YES, is this study investigator initiated? Yes

IF YES, answer questions # 13 and 14 IF NO, answer question # 13 only.

19 Are you using a drug/supplement/ food additive in a manner not approved by the FDA?

This drug was FDA approved in 2008 .

Labeled Indications

Postoperative ileus: To accelerate the time to upper and lower GI recovery following surgeries including partial bowel resection with primary anastomosis.Pharmacologic Category

- Gastrointestinal Agent, Miscellaneous
- Opioid Antagonist, Peripherally-Acting

This study uses this drug for treatment of opioid-induced constipation.

IF YES, answer questions 13a-13f You may reference the non-IRB protocol to answer these questions.

13a. Describe pertinent animal data that is available regarding the toxicity/safety of this drug.

Animal Data: Reproduction studies were performed in pregnant rats at oral doses up to 200 mg/kg/day (about 68 to 136 times the recommended human oral dose based on body surface area) and at intravenous doses up to 10 mg/kg/day (about 3.4 to 6.8 times the recommended human oral dose based on body surface area) and in pregnant rabbits at intravenous doses up to 15 mg/kg/day (about 5 to 10 times the recommended human oral

dose based on body surface area), and revealed no evidence of impaired fertility or harm to the fetus due to alvimopan.

13b. Describe pertinent human data that is available regarding the toxicity/safety of this drug.
FDA approval of Entereg in 2008 is based on the results of five multicenter, randomized, double-blind, parallel-group, placebo-controlled studies: four in the US and one ex-US. The trials enrolled over 2,000 adult subjects undergoing partial large or small bowel resection surgery with primary anastomosis or total abdominal hysterectomy under general anesthesia.

Among ENTEREG-treated patients undergoing surgeries that included a bowel resection, the most common adverse reaction (incidence ≥1.5%) occurring with a higher frequency than placebo was dyspepsia (ENTEREG, 1.5%; placebo, 0.8%). Adverse reactions are events that occurred after the first dose of study medication treatment and within 7 days of the last dose of study medication or events present at baseline that increased in severity after the start of study medication treatment.

13c. Have there been any human deaths associated with this drug?
There are no deaths associated with Alvimopan in published clinical trials, or in the package insert.
13d. In how many humans has this drug been used previously?
This drug has been FDA approved and marketed since 2008. It has been used in thousands of humans.

13e. If this protocol will be used in children describe any previous use of this drug with children of a similar age range.
NO children will be included in this protocol

20. Do the following criteria apply? Check all that apply

___x__ The investigation is intended to be reported to FDA as a well-controlled study in support of a new indication for use or intended to be used to support any other significant change in the labeling for the drug;

___x__ If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is intended to support a significant change in the advertising for the product;

_____ The investigation does involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

If Not checked- explain why you believe the risk to subjects is not increased:

The drug has been marketed and used for clinical care since 2008, providing adequate safety data to believe there is no increased risk to the subject.

____ The investigation will be conducted in compliance with the requirements for institutional review set part in part 21CFR56 and with the requirements for informed consent set forth in part 21CFR50 ; and This item must be checked.

____ The investigation will be conducted in compliance with the requirements of 21CFR312.7 (Promotion and charging for investigational drugs)
This item must be checked.

15. Is this a post-marketing study? Yes

►**IF YES is the study required to be done by the FDA?** No

APPENDIX: Recruitment

Recruitment includes identifying, review of records to determine eligibility or any contact to determine a potential subjects interest in the study.

*The UVa HIPAA covered entity is composed of the UVa VP Office of Research, the Health System, School of Medicine, School of Nursing, Nutrition Services (Morrisons), the Sheila C. Johnson Center, the Exercise and Sports Injury Laboratory and the Exercise Physiology Laboratory.

1. How do you plan to <u>identify</u> potential subjects?

- To "identify" a potential subject refers to steps you plan to take to determine which individuals would qualify to participate in your study. This does NOT include steps to actually contact those individuals.
- If your study involves more than one group of subjects (e.g. controls and cases or subjects and caregivers) note below which groups are being identified by the given method.
- Check the methods you plan to utilize:

a.__x__ Chart Review/ Clinic Schedule Review/ Database Review from a database established for health care operations (departmental clinical database) or an Improvement Project (*e.g. Performance Improvement, Practice Improvement, Quality Improvement*).
<u>If you plan to obtain data from the UVa Enterprise Data Warehouse (EDW) please see option b below.</u>

<u>DHHS:</u> Study team requests Waiver of Consent to identify potential subjects.

<u>HIPAA:</u> Allowed under Preparatory to Research if PHI to be accessed.

<u>IMPORTANT</u>
Keep in mind that PHI in the medical record may only be accessed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*
--a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

b____ Review of a database that was established to keep data to be used for future research such as the CDR, departmental research database or use of data from a separate current active research protocol.
If you plan to obtain data from the UVa Enterprise Data Warehouse (EDW) you are required to submit your request to the CDR. The CDR staff will work with the EDW to obtain the data you need.

DHHS: Study team requests Waiver of Consent to identify potential subjects.

HIPAA: Allowed under Preparatory to Research if PHI to be accessed.

IMPORTANT
Keep in mind that PHI in the medical record may only be accessed by individuals who work under the UVa HIPAA covered entity; which means they who meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*
--a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

The information from which you are obtaining potential subjects must also have an IRB protocol approval. If this item is checked, enter the IRB # below.

IRB# _____

If obtaining information from the Clinical Data Repository (CDR) insert IRB # 10797

c. ____ Patients UVa health care provider supplies the UVa study team with the patients contact information without patients' knowledge.

DHHS: Study team requests Waiver of Consent to identify potential subjects.

HIPAA: Allowed under Preparatory to Research if PHI will be shared by the health care provider.

IMPORTANT
Keep in mind that PHI may only be given to individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*
--a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

d. ____ Patient obtains information about the study from their health care provider. The patient contacts the study team if interested in participating. (Health care provider may or may not also be the a member of the study team)

DHHS: NA
HIPAA: Allowed under Health Care Operations

If this choice is checked, check 3d-INDIRECT CONTACT below.

e. __X__ Potential subjects will not be directly identified. They will respond to an advertisement such as a flyer, brochure etc.

If this choice is checked, check 3d- INDIRECT CONTACT below.
DHHS & HIPAA: NA

f. _____ Potential subjects have previously signed a consent to have their name in a registry/database to be contacted for future studies of this type.

IRB# of registry/ database: _____

DHHS & HIPAA: NA

g. _____ Other: Specify Answer/Response:

If item # a, b or c is checked above and if this protocol involves the use of protected health information do you confirm the following to be true? yes

- The use or disclosure is sought solely to review protected health information as necessary to prepare the research protocol or other similar preparatory purposes.
- No PHI will be removed from the UVa covered entity.
- The PHI that the researcher seeks to use or access is necessary for the research purposes.

2. How will potential subjects be contacted?

To "contact" a potential subjects refers to the initial contact you plan to take to reach a potential subject to determine if they would be interested in participating in your study. This may include direct contact by such methods as by letter, phone, email or in-person or indirect contact such as the use of flyers, radio ads etc.

If your study involves more than one group of subjects (e.g. controls and cases or subjects and caregivers) note below which groups are being contacted by the given method.

Check the methods below you plan to utilize:

a. _____ Direct contact of potential subjects by the study team via letter, phone, direct e-mail. Members of study team ARE NOT health care providers of patients. Information will not be collected from psychotherapy notes.

Note: Letter, phone, direct email scripts must be approved by IRB prior to use. See IRB-HSR Website for templates.

DHHS/HIPAA: Study team requests a Waiver of Consent and Waiver of HIPAA Authorization to contact potential subjects.

IMPORTANT:

Keep in mind that if PHI was collected during the identification phase that contact with potential subjects may only be performed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:

- a UVa student working in the UVa HIPAA Covered Entity*
- a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

b._x___Potential subjects will be approached while at UVa Hospital or Health Clinic by a person who is NOT a member of their health care team. Information will not be collected from psychotherapy notes.

DHHS & HIPAA: Study team requests a Waiver of Consent and a Waiver of HIPAA Authorization to contact potential subjects.

IMPORTANT:
Keep in mind that contacting individuals in a clinical setting may only be performed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:
a UVa student working in the UVa HIPAA Covered Entity*
a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

You should share the following information with the potential subject:

- Your name
- Who you are: physician, nurse etc. at the University of Virginia.
- Why you want to speak with them
- Ask if you have their permission to explain the study to them
- If asked about how you obtained their information use one of the following as an option for response.
    - DO NOT USE THIS RESPONSE UNLESS YOU HAVE OBTAINED PERMISSION FROM THEIR UVa PHYSICIAN: Your doctor, Dr. insert name wanted you to be aware of this research study and gave us permission to contact you.
    - We obtained your information from your medical records at UVa.
    - Federal regulations allow the UVa Health System to release your information to researchers at UVa, so that we may contact you regarding studies you may be interested in participating. We want to assure you that we will keep your information confidential.
- IF THE PERSON SEEMS ANGRY, HESITANT OR UPSET, THANK THEM FOR THEIR TIME AND DO NOT ENROLL THEM IN THE STUDY. YOU MAY ALSO REFER THEM TO THE IRB-HSR AT 924-9634.

c.____Direct contact of potential subjects by the study team by approaching in person at UVa or via letter, phone, direct e-mail. Members of study team contacting potential subjects ARE health care providers of patients.

If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use.
See IRB-HSR Website for templates.

DHHS: Study team requests a Waiver of Consent to contact potential subjects
HIPAA: Allowed under Health Care Operations.

d.__X__ Indirect contact (flyer, brochure, TV, broadcast emails, patient provided info about the study from their health care provider and either the patient contacts study team or gives their healthcare provider permission for the study team to contact them.)

The indirect method used (flyer, brochure, TV, broadcast emails) must be approved by the IRB prior to use. The IRB does not need to review any type of script to use when the potential subject responds to the indirect method.

DHHS & HIPAA: NA

f. ____ Potential subjects are not patients. The study does not include obtaining subjects health information. Subjects will be contacted directly via email, phone, letter or presentation in group setting with consent then obtained individually in a private setting.

If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use.
See IRB-HSR Website for templates.

DHHS: Study team requests a Waiver of Consent to contact potential subjects.
HIPPA: NA

3. **Will any additional information be obtained from a potential subject during "prescreening"?**

Pre-screening for IRB purposes is the term used to describe activities PRIOR to obtaining Informed Consent and may not include any research procedures.

The activities may involve pre-screening of potential subjects over the telephone or in person is generally performed to determine their initial eligibility for, and, interest in a study and is a common strategy in the recruitment process.

Questions appropriate for pre-screening address the specific inclusion/exclusion criteria for the study and other issues of suitability, for example, an individual's ability to come to the research site multiple times.
It is not appropriate at this point in the process (i.e. prior to obtaining informed consent/enrollment) to gather information that is not directly related to assessing eligibility and suitability (e.g. obtaining complete medical histories, obtaining blood specimens for lab tests).
An additional telephone script is not required, for this pre-screening process, in addition to any scripts required under Recruitment question # 2.

Answer/Response: Yes "What do you use for pain control and how often do you take it?" is the only pre-screening question that will be asked.

IF YES, submit any documents that will be used to collect pre-screening information so that the IRB may confirm what questions will be asked.
NOTE: To comply with HIPAA regulations only the minimum necessary information may be collected at this time. This means that only questions pertaining to the Inclusion and Exclusion Criteria may be asked.

IF YES,
DHHS: study team requests a Waiver of Documentation of Consent for Pre-screening questions.

HIPPA:
HIPAA does not apply if:
--no PHI is collected or
--if PHI is collected from a potential subject by an individual from a department that is not part of the HIPAA covered entity.

HIPAA does apply if the collection occurs by individuals* who work in a department that is part of the HIPAA covered entity.

In this case the collection will be covered under Health Care Operations/

These individuals are those that meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*
--a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

IF YES, Will any of the questions involve health information?
Answer/Response: "What do you use for pain control and how often do you take it?" is the only pre-screening question that will be asked.

IF YES, will you collect HIPAA identifiers with the health information?
Answer/Response: YES

IF YES, which HIPAA identifiers will be recorded?
Answer/Response: MRN

Do you confirm that health information with HIPAA identifiers will not be shared outside of UVa until a consent form is signed or only shared in a de-identified manner?
Answer/Response: Yes

4. **Do you plan to ask the subjects to do anything, other than answering questions, for the study prior to signing a consent?** No

5. **How will the consenting process take place with either the prospective subject, the subject's legally authorized representative or parent/legal guardian of a minor (if applicable)?**

HIPPA:
If the individual, obtaining consent, works under the HIPAA Covered Entity consenting is covered under Health Care Operations.

If the individual obtaining consent does not work under the HIPAA covered entity, HIPAA does not apply.

Potential subjects will be approached at their surgical work up in the clinic, in PETC, SAS(day of surgery) or in the hospital (if inpatients). Once a potential subject is identified, they will be interviewed in a quiet and private place and may have family or friends with them if they choose. If there is concern that the potential subject may not be able to read the potential subject will be asked to read the first sentence of the consent form to determine if they are capable of reading. Depending on the response they will either be offered the opportunity to read the consent form or have the consent form read to them. Once the consent has been read the person obtaining consent will summarize the consent form verbally, asking open ended questions to determine if the potential subject understands what is being covered in the consent form. Questions might include:

- Would you summarize for me what you believe will be done to you if you are in this study?
- Would you benefit from this study?
- What do you feel are the risks of being in this study?

Potential subjects will be given an opportunity to ask questions. Their level of understanding will dictate how much time will be spent covering each item. Once all of their questions have been answered, if they decide to participate, they will be asked to sign the consent form.
The person obtaining consent will sign the form and subjects will be given a copy of the signed consent form. Study procedures will then begin. The informed consent process for each individual subject will be documented in the subject's medical record.

6. Will subjects sign a consent form for any part of the study? Yes

7. Will the study procedures be started the same day the subject is recruited for the study?

Yes

►IF YES, explain in detail why the subject cannot be given more time to make a decision to consent.

The study is moderate risk and will be easily explained to the potential subject on the day the study procedures are started.
Potential subjects are not always seen by study team prior to day study procedures are started. Patients are scheduled for clinical procedures/surgery by health care providers other than study team members. The potential subject will be provided adequate time to read the consent and consider their options.

►IF YES, explain in detail what will be done to assure the potential subject has enough time to make an informed decision.

Study staff will review the study specifics and reconfirm intent to participate when the subject presents for surgery. Potential subjects will be given an opportunity to ask questions. Their level of understanding will dictate how much time will be spent covering each item. Once all of their questions have been answered, if they decide to participate, they will be asked to sign the consent form

8. Is there the potential to recruit economically or educationally disadvantaged subjects, or other vulnerable subjects such as students or employees?

Yes

IF YES, what protections are in place to protect the rights and welfare of these subjects so

All subjects will be informed that participation is voluntary and that participation will not affect their status as a student or employee.

9. Do you need to perform a "dry run" of any procedure outlined in this protocol? No

Privacy Plan

The following procedures must be followed.

- The data will be secured per the Data Security Plan of this protocol.
- Only investigators for this study and clinicians caring for the patient will have access to data. They will each use a unique login ID and password that will keep confidential. The password should meet or exceed the standards described on the Information Technology Services (ITS) webpage about *The Importance of Choosing Strong Passwords.*
- Each investigator will sign the University's Electronic Access Agreement forward the signed agreement to the appropriate department as instructed on the form.

  If you currently have access to clinical data it is likely that you have already signed this form. You are not required to sign it again.
- UVa University Data Protection Standards will be followed

http://www.virginia.edu/informationsecurity/dataprotection.

- If identifiable data is transferred to any other location such as a desktop, laptop, memory stick, CD etc. the researcher must follow the University's "Electronic Storage of Highly Sensitive Data Policy". Additional requirements may be found in the University's Requirements for Securing Electronic Devices.
- If identifiable data is taken away from the UVa Health System, Medical Center Policy # 0218 will be followed.
- Data will be securely removed from the server/drive, additional computer(s), and electronic media according to the University's Electronic Data Removal Policy.
- Data will be encrypted or removed if the electronic device is sent outside of UVa for repair according to the University's Electronic Data Removal Policy.
- If PHI will be faxed, researchers will follow the Health System Policy # 0194.
- If PHI will be emailed, researchers will follow the Health System Policy # 0193 and University Data Protection Standards .
- Data may not be analyzed for any other study without additional IRB approval.
- If you are using patient information you must follow Health System Policy # 0021.
- Both data on paper and stored electronically will follow the University's Record Management policy and the Commonwealth statute regarding the Destruction of Public Records.

Summary of Requirements to Comply with UVa Health System, Medical Center and University Policies and Guidance as noted above:

Highly Sensitive Data is:
-personal information that can lead to identity theft if exposed or
-data that reveals an individual's health condition and/or history of health services use.
Protected Data (PHI) a type of Highly Sensitive Data, is data combined with a HIPAA identifier
Identifiable Data under HIPAA regulations is considered to be *Highly Sensitive Data at UVa.*
A **Limited Data Set** (LDS) under HIPAA regulations is considered to be *Moderately Sensitive Data* at UVa. The only HIPAA identifiers associated with data: dates and or postal address information limited to town or city, state, and zip code.
Will not include subjects age if older than 89 or subjects DOB if older than 89.

Highly Sensitive Data (Identifiable Health Info per HIPAA)	**Moderately Sensitive Data (Limited Data Set and De-identified data per HIPAA)**
General Issues	*General Issues*
Discussions in private Do not share with those not on the study team or those who do not have a need to know.	Do not share with those not on the study team or those who do not have a need to know
Password protect	Password protect
Physically secure (lock) hard copies at all times if not directly supervised. If not supervised hard copies must have double protection (e.g. lock on room OR cabinet AND in building requiring swipe card for entrance).	Physically secure (lock) hard copies at all times if not directly supervised.
For electronic documents turn off File Sharing; turn on firewalls; use up to date antivirus and antispyware; delete data securely.	For electronic documents turn off File Sharing; turn on firewalls; use up to date antivirus and antispyware; delete data securely.
Encrypt See Encryption Solutions Guidance *Files on Health System Network drives are automatically encrypted. If not stored there it is study teams responsibility to make sure data are encrypted.*	
If device sent out for service or repair, encrypt or remove data AND contract for repair using a UVa Purchase order.	If device sent out for service or repair, encrypt or remove data AND contract for repair using a UVa Purchase order.
Store files on a network drive specifically designated for storing this type of data, e.g. high-level security server/drives managed by Information Technology Services or the “F” and “O” managed by Heath Systems Computing Services. You may access it via a shortcut icon on your desktop, but you are not allowed to take it off line to a local drive such as the desktop of your computer (e.g. C drive) or to an individual Use Device*. May access via VPN	
Do not share with sponsor or other outside group before consent is obtained or the IRB has granted appropriate approvals and contract/ MTA is in place	Do not share with sponsor or other outside group before consent is obtained or the IRB has granted appropriate approvals and contract/ MTA is in place
If collected without consent/ HIPAA authorization will NOT be allowed to leave UVa HIPAA covered entity unless disclosure is approved by the IRB and the disclosure is tracked in EPIC	If collected without consent/ HIPAA authorization will NOT be allowed to leave UVa HIPAA covered entity unless disclosure is approved by the IRB and an MTA is in place prior to sharing of data

Highly Sensitive Data (Identifiable Health Info per HIPAA)	**Moderately Sensitive Data (Limited Data Set and De-identified data per HIPAA)**
Electronic Data Collection & Sharing	*Electronic Data Collection & Sharing*
(e.g. smart phone app, electronic consent using tablet etc.) MUST consult with ISPRO or Health System Web Development Office: 434-243-6702 ▪ University Side: IT-Security@virginia.edu ▪ Health System: Web Development Center:	
Individual-Use Device	*Individual-Use Device*
Do not save to individual-use device* without written approval of your Department AND VP or Dean. If approval obtained, data must be password protected and encrypted.	
Do not save an email attachment containing HSD to an individual use device (e.g. smart phone)	
E Mail	*E Mail*
Do not share via email with Outlook Web/ or forward email using other email vendors like Gmail/ Yahoo	
Do not send via email on smart phone unless phone is set up by Health System	
Email may include name, medical record number or Social Security number only if sending email to or from a person with * HS in their email address. *NOTE: VPR & IRB staff do not meet this criteria!*	In addition to sharing LDS, may include initials if persons sending and receiving email work within the UVa HIPAA covered entity.**
FAX	*FAX*
Verify FAX number before faxing	Verify FAX number before faxing
Use Fax Cover Sheet with Confidentiality Statement	Use Fax Cover Sheet with Confidentiality Statement
Verify receiving fax machine is in a restricted access area	Verify receiving fax machine is in a restricted access area
Verify intended recipient is clearly indicated	Verify intended recipient is clearly indicated
Recipient is alerted to the pending transmission and is available to pick it up immediately	Recipient is alerted to the pending transmission and is available to pick it up immediately

Highly Sensitive Data (Identifiable Health Info per HIPAA)	**Moderately Sensitive Data (Limited Data Set and De-identified data per HIPAA)**
Electronic Data Collection & Sharing	*Electronic Data Collection & Sharing*
(e.g. smart phone app, electronic consent using tablet etc.) MUST consult with ISPRO or Health System Web Development Office: 434-243-6702 ▪ University Side: IT-Security@virginia.edu ▪ Health System: Web Development Center:	
Individual-Use Device	*Individual-Use Device*
Do not save to individual-use device* without written approval of your Department AND VP or Dean. If approval obtained, data must be password protected and encrypted.	
Do not save an email attachment containing HSD to an individual use device (e.g. smart phone)	
E Mail	*E Mail*
Do not share via email with Outlook Web/ or forward email using other email vendors like Gmail/ Yahoo	
Do not send via email on smart phone unless phone is set up by Health System	
Email may include name, medical record number or Social Security number only if sending email to or from a person with * HS in their email address. *NOTE: VPR & IRB staff do not meet this criteria!*	In addition to sharing LDS, may include initials if persons sending and receiving email work within the UVa HIPAA covered entity.**
FAX	*FAX*
Verify FAX number before faxing	Verify FAX number before faxing
Use Fax Cover Sheet with Confidentiality Statement	Use Fax Cover Sheet with Confidentiality Statement
Verify receiving fax machine is in a restricted access area	Verify receiving fax machine is in a restricted access area
Verify intended recipient is clearly indicated	Verify intended recipient is clearly indicated

Highly Sensitive Data (Identifiable Health Info per HIPAA)	**Moderately Sensitive Data (Limited Data Set and De-identified data per HIPAA)**
Electronic Data Collection & Sharing	*Electronic Data Collection & Sharing*
(e.g. smart phone app, electronic consent using tablet etc.) MUST consult with ISPRO or Health System Web Development Office: 434-243-6702 University Side: IT-Security@virginia.edu Health System: Web Development Center: Contract must include required security measures.	
May NOT be stored in places like UVaBox, UVaCollab, QuestionPro. May also NOT be stored in non-UVa licensed cloud providers, such as Dropbox, Google Drive, SkyDrive, Survey Monkey, etc.	May be stored in places like UVaBox, UVaCollab, QuestionPro. May NOT be stored in non-UVa licensed cloud providers, such as Dropbox, Google Drive, SkyDrive, Survey Monkey, etc.
LOST OR STOLEN:	*LOST OR STOLEN:*
Must report in accordance with protocol/ in accordance with the Information Security Incident Reporting Policy. Any data breach will also be reported to the IRB of Record if the report meets the criteria of an Unanticipated Problem.	Must report in accordance with protocol/ in accordance with the Information Security Incident Reporting Policy. Any data breach will also be reported to the IRB of Record if the report meets the criteria of an Unanticipated Problem.

** Individual Use Device – examples include smart phone, CD, flash (thumb) drive, laptop, C drive of your computer,*
***The UVa HIPAA covered entity is composed of the UVa VP Office of Research, the Health System, School of Medicine, School of Nursing, Nutrition Services (Morrison's), the Sheila C. Johnson Center, the Exercise and Sports Injury Laboratory and the Exercise Physiology Laboratory.*

APPENDIX: Support Source

- **Describe what will be provided and by whom**.

Merck will provide study drug and placebo
Merck will receive data prior to publication, however will not be taking on the liability of sponsor

- **Do you confirm that you will obtain a contract/ material transfer agreement with the provider via the Medical Center Procurement office or Office of Sponsored Programs (OSP)** ospnoa@virginia.edu**?**
  Yes

APPENDIX: Transfer of Data Outside of UVa

INSTRUCTIONS: Do not complete this section if the only data being sent out is being sent/shared with specimens.

1. **Who will data be sent to/shared with?**
   De-identified data will be shared with the statistician.
   The sponsor will only review the completed article prior to publication.

2. **What identifiers will be sent with/shared with the data? No identifiers will be sent to either the statistician or the sponsor.**

Table A: Identifiers per HIPAA under 164.514(b)(2)(i) and (ii)

YES	NO	
	X	1. Name
	X	2. All geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of the zip code if, according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same 3 initial digits contains more than 20,000 people and (2) The initial 3 digits of a zip code for all such geographic units containing 20,000 is changed to 000.
	X	3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older. *[This means you may record the year but not record the month or day of any date related to the subject if the subject is under the age of 89. In addition if the subject is over the age of 89 you may not record their age and you may not record the month, day or year of any date related to the subject]*
	X	4. Telephone numbers
	X	5. Fax numbers
	X	6. Electronic mail addresses
	X	7. Social Security number
	X	8. Medical Record number
	X	9. Health plan beneficiary numbers
	X	10. Account numbers
	X	11. Certificate/license numbers
	X	12. Vehicle identifiers and serial numbers, including license plate numbers
	X	13. Device identifiers and serial numbers
	X	14. Web Universal Resource Locators (URLs)
	X	15. Internet Protocol (IP) address numbers
	X	16. Biometric identifiers, including finger and voice prints
	X	17. Full face photographic images and any comparable images
	X	18. Any other unique identifying number, characteristic, code that is derived from or related to information about the individual (e.g. initials, last 4 digits of Social Security #, mother's maiden name, first 3 letters of last name.)
	X	19. Any other information that could be used alone or in combination with other information to identify an individual. (*e.g. you share the KEY to the CODE (not just the code), subject has a rare disease etc.)*

Table B:
Will you share either of the following?

YES	NO	

	x	1. Postal address information, other than town or city, state, and zip code (e.g. house number / street address / GPS)
	x	2. Age if over the age of 89 OR Date of Birth if over the age of 89

If you answered YES to any item in Table A, except item # 2 or 3, OR answered YES to an item in Table B, the data will be considered identifiable. Tracking of disclosures will be required unless it is noted in the consent form that data will be shared with the entity noted AND that consent is obtained prior to sharing of data.

If you answered Yes to only Item 2 or 3 in Table A and No to both items in Table B, the data you are sharing is considered a Limited Data Set.
A Data Use Agreement will be required in the contract/MTA.

3. **Do you confirm that you will obtain a contract/ material transfer agreement with whomever you are sharing data with outside of UVa via the School of Medicine Grants and Contracts Office or the Office of Sponsored Programs (OSP)** ospnoa@virginia.edu**?** Answer/Response: Yes