Locally applied antibiotics for infection prophylaxis in treatment of open fractures

NCT03705962

06 Dec 2016

Protocol with Statistical Analysis Plan

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 is leaving 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 PI of this study, Seth Yarboro MD is Assistant Professor of Orthopedic Surgery, Division of Trauma at University of Virginia. He has extensive experience with treatment of Orthopedic Trauma cases and clinical research. He studied the application of local antibiotics to open wounds in rat model with favorable results and is now planning to conduct a clinical trial using aqueous tobramycin for infection prophylaxis in open fractures. Such extensive experience and knowledge base puts him at a unique position to undertake the current study.

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

The primary objective of this study is to investigate the effectiveness of local antibiotic versus placebo in the prevention of infections in open fractures. The study will assess whether local treatment of open fractures with the antibiotic tobramycin (in addition to standard systemic antibiotics) will decrease the risk and rate of infection, time to fracture union, and rate of re-operation. This will be studied using a randomized controlled clinical trial design in adult population of age 18-70 years who present with open fractures. About 133subjects will be recruited in this study at UVA. There will also be similar studies performed at University of Florida- Jacksonville and Medical University of South Carolina and we will be performing a collaborative site analysis study with those centers and we will be sharing demographic, infection and treatment information (at either 2 or 6 weeks), and any adverse events that occur.

Note: Standard protocols at UVA will be followed for systemic antibiotic administration. No specimens will be collected for research purposes. The patient will otherwise receive the standard of care treatment for their fractures.

SAFETY SUMMARY:

- Local tissue safety: 80mg/40mL is 2 mg/mL (which is 2000micrograms / mL). This level was found to be safe in Rathbone/Wenke study (1). Further, the local level is expected to decrease quickly, as opposed to the sustained levels seen in tissue culture in that study.

- Systemic safety: Gentamicin/tobramycin is routinely given as a single IV dose at 4-7mg/kg (depending on severity of infection). For a 70kg patient treated with 5mg/kg dose, 350mg would be given IV (thus immediately available systemically). The dose we administer is only 80mg, a much lower dose, and is administered in the wound (thus more similar to IM than IV). Peak levels are not routinely checked at UVA for short courses of even the higher doses of IV tobramycin/gentamicin, and we find no safety issue or support for obtaining peak levels in this study. Systemic levels high enough to cause side effects are typically associated with dosing that is higher than recommended or too frequent to allow adequate renal clearance.

- In cases of renal impairment, dosing is typically spaced out further to allow time for renal clearance (see attached below from Stanford Guidelines 2013). This would not create a safety issue in our study, as a single 80mg dose is administered. If ongoing therapy with a systemic aminoglycoside is required (either gentamicin or tobramycin), the patient's primary team would be made aware of the intra-operative dose and follow serum levels as appropriate based on repeated dosing.

- This route of administration of local tobramycin represents the current standard of care in my practice. I have treated all open fractures this way since starting at UVA in 2012, and have observed no adverse effects. In fact, my impression is that the infection rate is lower as a result of this practice.

Unpublished pilot data from a single trauma surgeon at UNC Chapel Hill demonstrated a significantly lower infection rate in patients treated with local aminoglycoside (initially gentamicin, then changed to tobramycin once above Wenke data showing lower potential for local toxicity was published). In the comparison group (received no local antibiotics) the overall incidence of deep infection was 4.8% (11/243) while in the current group it was 0.6% (2/343, p=0.0025). Looking specifically at patients treated with ORIF found a historical deep infection rate of 6% (8/134) versus 1.2% (2/170, p=0.0247) in the local antibiotic group. Tibia fractures had a historical deep infection rate of 10% (3/30), and there were no infections in the local antibiotic group (0/56, p=0.0397). For open fractures, the historical group had 19% (5/26) infection rate versus none (0/34) in the local antibiotic group (p=0.012).

Background

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

Local antibiotics provide high local concentrations with lower systemic levels than parenterally administered antibiotics. The delivery of local antibiotics can both supplement and sometimes obviate the need for systemic antibiotics. In certain instances, the target area of treatment may be avascular, preventing systemic antibiotics from reaching the targeted site. In these scenarios, local antibiotics may serve as the only effective option in treating the infection. Perhaps the main advantage of local antibiotic therapy is the ability of an antibiotic to reach a high local concentration while simultaneously having a low or undetectable systemic concentration, thereby avoiding certain negative side effects such as nephrotoxicity and ototoxicity and decreasing the chances of developing pathogenic resistance.[2-4] At this high level of local concentration, many bacteria that might otherwise be normally resistant to an antibiotic fall within its spectrum of activity.[5]

Antibiotics can be effectively administered in aqueous solution, and do not necessarily require a carrier. While antibiotic (as well as antiseptic) solutions have been used for many years, there is clinical data that suggest this method of delivery is effective. A significant positive impact was shown in a series of shoulder arthroplasty patients, where the rate of infection was decreased by one order of magnitude with intra-articular injection of aqueous gentamicin performed after wound closure.[6] This method of administration has also been effective in a rat model, where aqueous gentamicin was significantly better for infection prophylaxis after placement of a metal implant and contamination with Staphylococcus aureus, and this effect was further improved by concomitant administration of systemic antibiotics.7,8] This method of delivery is distinct from antibiotic solution for irrigation, as the aqueous antibiotic is injected into the surgery site after the wound is closed. An 18 ga needle is used adjacent to the incision to inject the solution throughout the wound. This technique allows the solution to ideally infiltrate the interstices or depths of the wound. In practice, the solution has been made in a concentration of 2 mg/mL (80 mg aminoglycoside in 40 mL injectable saline). Recent data which suggested lower local cytotoxicity with tobramycin compared to gentamicin [5] has led us to choose tobramycin in this application. We will therefore use tobramycin as the study drug in this protocol.

The advantages of delivering antibiotic in aqueous form are several, including cost, as there is no need for a specialized vehicle of delivery. The antibiotic drugs are approved and ready for use this time. Also, the wound encounters a higher maximum antibiotic concentration, potentially improving antibiotic efficacy.

Drawbacks to this method may include poor sustained antibiotic level. However, other vehicles for delivery such as collagen sponge have been shown to elute the drug very quickly, then potentially become a

foreign body at the surgical site. Thus, this method of antibiotic delivery may be more effective in a situation where sustained delivery is not required, such as prophylaxis of surgical site infections.

Regarding local toxicity and safety, Rathbone et al demonstrated levels of toxicity for many commonly used antibiotics.[1] This data is helpful for determining appropriate concentrations that are acceptable in the wound cavity, regardless of the delivery method. Upon evaluating osteogenic cell viability and activity as measured by alkaline phosphatase activity, wide variability was noted, even within families of antibiotics. Rifampin, tetracyclines, and ciprofloxacin were noted to be particularly cytotoxic, with considerable decrease in cell number and activity at concentrations of even 100mcg/mL. Tobramycin, vancomycin, and amikacin were noted to be least cytotoxic. Of note, cell number and activity were measured at time points of 10 and 14 days for various concentrations of each antibiotic. While the response of osteogenic cells to these concentrations of antibiotics is useful information, it should be noted that these are measured in response to sustained levels of antibiotics, and in the clinical setting the antibiotics levels are highest at early time points then often decrease rapidly.

Hypothesis to be Tested

Local aqueous tobramycin used for infection prophylaxis injected into open fracture wounds following definitive closure prevent infections, and decreases re-operation rate in patients with open fractures within 6 weeks of administration.

Study Design: Biomedical

1. Will controls be used? Yes

►IF YES, explain the kind of controls to be used.
We will use placebo controls who will receive 40 mL of 0.9% NS injected into the closed wound at the end of surgical treatment.

2. What is the study design?
Double blind

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

►IF YES, provide a justification for the use of a placebo
This study will need placebo group to evaluate the effectiveness of local injection of tobramycin.

Human Participants

Ages: 18-70
Sex: **Both**
Race: **All**

Subjects- see below

1. Provide target # of subjects (at all sites) needed to complete protocol. 133

2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites.

Approximately, 20% of subjects will be lost to follow up

3. **How many subjects will be enrolled at all sites?** 133

4. **How many subjects will sign a consent form under this UVa protocol? 133**

5. **Provide an estimated time line for the study.**2 years

Inclusion/Exclusion Criteria

1. **List the criteria for inclusion**
   - Ages 18 – 70 years
   - Gustilo Type I,II,IIIa open fracture (s)
   - Ability to provide informed consent (or proxy consent in cases where subject is temporarily impaired when intubated and sedated)
   - Subject should be able to follow up at the scheduled times following surgery
   - Subjects who may have compartment syndrome, renal insufficiency, and those who are immunosuppressed regardless of antibiotic administration will also be included in the study
   -

2. **List the criteria for exclusion**
   - Closed fracture
   - Severe injury requiring flap coverage or vascular reconstruction (Gustilo-Anderson Type IIIB and C respectively)
   - Aminoglycoside allergy
   - Presentation greater than 48 hours after injury
   - Pathologic fracture
   - Preexisting infection in bone with an open fracture
   - Patients with multiple trauma involving liver, kidney, or brain
   - Pregnancy (self-reported)
   - Current status as prisoner

3. **List any restrictions on use of other drugs or treatments**.

Any other antibiotic not related to open fracture is prohibited during the study, which could mask wound infection.

Statistical Considerations

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

►IF YES, describe the stratification/ randomization scheme.

Subjects will be randomized prior to surgical treatment. Randomization will be double blind. Neither the subject nor the surgeon injecting the antibiotic or placebo know which arm the subject belongs to. The Medical Pharmacist or Joe Hart PhD will have the key to randomization, at UVA. The other sites involved will be expected to manage their randomization scheme. UVA will not oversee the other sites.

►**IF YES, who will generate the randomization scheme?**
__X___ Other*:* Wendy Novicoff PhD

2. What are the statistical considerations for the protocol?

- This is a prospective, randomized double blind study. Subjects will be randomized to antibiotic (80mg tobramycin/40mL saline) or placebo arm (40mL of 0.9% saline).

- The primary objective of this study is to evaluate the efficacy of local antibiotics in decreasing incidence of infection. The primary outcome will include evidence of infection in the first 6 weeks of surgery. Infection will be defined as major and minor, with major indicated by return to the operating room for irrigation and debridement. Minor infection is represented by documentation of cellulitis or superficial infection at surgical site and administration of oral antibiotics. .

- Superficial infection as indicated by documentation of cellulitis at surgical site and administration of oral antibiotics with the indication of wound problems. The primary purpose of this study is to document infection rates in the first 6 weeks after surgery. If an infection is found, it will be cared for per standard clinical care; however, it will not be followed for research purposes.

- There will be no contingencies for early stopping as the patients are receiving a single dose of antibiotics. There will be no interim analysis or stratification factors

- We expect approximately - 60 – 65 open fractures within a year to be treated at UVA based on historical records.

We will use a one-sided test for proportions to compare the control and experimental groups for the primary endpoint (presence of infection) and the secondary endpoint of evidence of non-union. A p-value less than 0.05 will be considered a significant result.

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

A sample size analysis was completed for different alpha and power levels. A one-sided test for proportions was chosen to compare the baseline (no treatment) group to the hypothesized proportion (treatment group); based on historical data, we assumed that the no treatment group would have a 10% infection rate, and the treatment group would have a 1% infection rate. Using an alpha of 0.05 and power of 70%, we would need to have 60 patients in each group.

With an expected accrual rate of 65 patients per year, we would expect to enroll 130 patients in two years. In order to maintain the sample size needed to ensure statistically valid results, we would want to enroll approximately 133 patients over the study period to end up with at least 120 patients in the analysis.

4. What is your plan for primary variable analysis?
One-sided test for proportions

5. What is your plan for secondary variable analysis?
N/A. We are only conducting a primary analysis.

6. Have you been working with a statistician in designing this protocol? Yes
IF YES, what is their name? Joe Hart

Will data from multiple sites be combined during analysis? Yes

Information from Outside Institution

INSTRUCTIONS:
You will need to submit an IRB approval or documentation from the outside institution documenting that they approve of this study being done at their site and info being shared with UVa.
In order to obtain information from other sites in the future, you will be required to submit a modification of this protocol to the IRB-HSR.

1. **List the names of outside institutions that will be supplying data and/or specimens for this study.**
   Answer/Response: University of Florida-Jacksonville. Medical University of South Carolina

2. **Describe the type of information you will receive from each site.**
   Answer/Response: We will receive de-identified subject demographics, infection information, pertinent dates, surgical procedures performed, and information re: treatment

3. Does the outside institution have an IRB?
Answer/Response: Yes.

IF NO, list the names of the individuals who will be supplying the data and/or specimens.
INSTRUCTIONS: You will be required to submit a signed Unaffiliated Investigator Agreement for each person listed.
Answer/Response:

Biomedical Research

1. What will be done in this protocol?

Patients who present with open fractures to UVA Health System will be approached for participation in the study. After obtaining Informed consent, subjects will be randomized to Antibiotic Arm (experimental) or Placebo. Administration of the local antibiotic in this study is being done solely for answering a research question on the efficacy of the antibiotic tobramycin in decreasing the risk and rate of infection.

Subjects will be randomized to the experimental group, who will be injected locally at the wound cavity (i.e. fracture site, surrounding soft tissue which include muscle, and subcutaneous space) with 80mg/40mL of tobramycin after wound closure, and placebo group who will be injected locally with 40 mL 0.9% NS after wound closure. Systemic antibiotic will not be withheld and will be done along side the local injection of tobramycin. If patient returns to the OR for repeat debridement procedures, the injection will be repeated. If patient returns to the OR for repeat debridement procedures, the injection will be repeated. The second injection will only be given if the subject undergoes a repeat procedure, and will be given two days later than the first injection. By this time, serum tobramycin levels would have normalized, given the low does and time interval. . Dose volume will not be adjusted because the safety of this antibiotic assumes that the patient weights at least 16 kg, and any patient 18 years or older will weigh more than that. While systemic antibiotic treatment is standard of care, animal studies and early clinical case series data indicated that injection of aqueous aminoglycoside after wound closure locally could be a highly effective technique for wound infection prophylaxis[1]. In this study protocol, other aminoglycosides (eg. Gentamycin) will be allowed as part of standard systemic prophylaxis.

Follow up data will be collected at 2 weeks, 6 weeks. Clinical data will be collected from medical records

2. List the procedures, in bullet form, that will be done for <u>RESEARCH PURPOSES</u> as stipulated in this protocol.

- Medical record review at baseline and all subsequent study weeks up to 1 year after surgery
- Randomization to Antibiotic (tobramycin) arm or Placebo before surgery by clinical pharmacy program at UVA.
- Experimental group will have the close wound injected with 80 mg/40mL of tobramycin at the END of surgery
- Control group will have 40 mL 0.9%NS injected into the closed wound at the end of the case
- Follow up at 2 and 6 weeks at the clinic. *These visits to the clinic will coincide with the follow up as in standard of care for open fracture management.*

3. 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

4. Will any of the procedures listed in item # 2 have the potential to identify an incidental finding? This includes ALL procedures, assessments and evaluations that are being done for <u>RESEARCH PURPOSES</u> that may or may not be considered investigational. yes

►IF YES, *check one of the following two options:*

___x__The examination(s) utilize(s) the same techniques, equipment, etc., that would be used if the subject were to have the examination(s) performed for clinical care. **There exists the potential for the discovery of clinically significant incidental findings.**

- The PI takes full responsibility for the identification of incidental findings:
- The PI will inform the subjects verbally of all incidental findings that are of clinical significance or are of questionable significance**.**
- A follow-up letter describing the finding should be provided to the subject with instructions to either show the letter to their PC or if the subject has no PCP, the subject should be instructed to make an appointment at UVa or at the Free Clinic**.**

5. Do any of the procedures listed above, under question # 2, utilize any imaging procedures for <u>RESEARCH PURPOSES</u>? No

6. Will you be using viable embryos? NO
Will you be using embryonic stem cells? NO

7. **Are any aspects of the study kept secret from the participants?** NO

Is any deception used in the study? NO

If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study. **NA**

Collaborative Site Analysis Studies

1. **List the sites that will be sharing data/specimens**.
   - University of Florida- Jacksonville
   - Medical University of South Carolina (MUSC)

2. **Will any data/specimens be sent to UVa for analysis from the sites outside of UVa?**
   Only data. There will be no data sent from UVA to other sites, data will only flow TO UVA.
   ►**IF YES, do you confirm you will have received a copy of the IRB approval from the outside site before receiving data/specimens from them?** Yes, confirmed.

3. **Do you confirm you will have a Material Transfer Agreement (MTA) through the Grants and Contracts office prior to sending or receiving data/specimens?** Yes, confirmed

4. **Describe the process for sharing safety concerns.** We will have conference calls no less than twice per year. If a SAE occurs and if it is deemed unexpected AND related there will be a conference call within 5 days with the site-PI's.

INSTRUCTIONS

- e.g. weekly conference calls, use of SAE forms, overall safety monitor etc.

- include frequency of communication
- identify participants (by role) in this process

Collaborative Site Analysis Studies DSMP			
Type of Event	**To whom will it be reported:**	*Time Frame for Reporting*	*How reported?*
***Serious, unexpected and related or possibly related adverse events**	All Research Sites	Within 15 days after the site PI receives knowledge of the event.	IND/IDE Safety Report (Cover letter, copy of MedWatch/narrative)
***Unanticipated Problem**	All Research Sites	Within 15 calendar days from the time the Site PI receives knowledge of the event.	Letter to Participating PIs, Copy of MedWatch or narrative
Protocol Violations/Noncompliance *The IRB-HSR only requires that MAJOR violations be reported, unless otherwise required by the sponsor.*	All Research Sites	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.*

**as defined in each sites protocol*

Data and Safety Monitoring Plan.

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 **even if the event is not 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

1.4 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.

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

1.5 If pregnancy occurs how will this information be managed?

___X__ Adverse Event- will follow adverse event recording and reporting procedures outlined in section 3.

1.6 What is the definition of a Protocol Enrollment Exception?

___X__NA- No outside sponsor

1.7 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**
Nephrotoxicity	____Occurs frequently ____Occurs infrequently _X___Occurs rarely ____Frequency unknown
Neurotoxicity manifested by ototoxicity – vestibular and auditory	____Occurs frequently ____Occurs infrequently _X___Occurs rarely ____Frequency unknown
Neurotoxicity manifested by numbness, skin tingling, muscle twitching and convulsions (in patients with preexisting renal damage and normal renal function with prolonged exposure to tobramycin	__ X Occurs frequently ____Occurs infrequently _ ___Occurs rarely ____Frequency unknown
Nephrotoxicity in patients with impaired renal function and in those who received high dose of tobramycin for prolonged period	__X__Occurs frequently ____Occurs infrequently _ ___Occurs rarely ____Frequency unknown
Violation of subject's privacy and confidentiality	Minimized due to the requirements of the privacy plan in this protocol

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

- Renal and eighth cranial nerve function will be closely monitored, especially in patients with known or suspected reduced renal function at onset of therapy and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy.
- Urine will be examined for decreased specific gravity, increased excretion of protein and the presence of cells or casts.

- Blood urea nitrogen (BUN), serum creatinine or creatinine clearance will be determined per standard of care during hospitalization.
- Evidence of ototoxicity (dizziness, vertigo, tinnitus, roaring in the ears or hearing loss) or cephrotoxicity will prompt closer monitoring and consultation of ENT and/or the nephrology teams.
- Concurrent and/or sequential systemic or topical use of other potentially neurotoxic and nephrotoxic drugs including: cisplatin, cephaloridine, kanamycin, amikacin, neomycin, polymyxin B, colistin, paromomycin, streptomycinvancomycin, and viomycin will be avoided. Age and dehydration which increase the risk of toxicity will be monitored. Concurrent use of tobramycin with potent diuretics such as ethacrynic acid or furosemide will be avoided. All patients on diuretics will have them held on the day prior to surgery to avoid complications. Diuretics will be withheld after subject signs Informed consent
- Injecting the drug directly into the fracture site will pose no greater than risk than intramuscular injection of tobramycin.

Clinical care team will be notified of the need to avoid other potentially nephrotoxic or neurogenic agents. A note will be put in Epic to this effect.

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

__X___Treatment would be stopped if the subject had a serious adverse event deemed related to study, or study drug will be increased if the subject tolerates dosing

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

__X___Per IRB, PI, DSMB, or sponsor discretion

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

__X___Other: Confidentially compromised

2.6 **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 deemed related/possibly related to study

3.2 How will adverse event data be collected/recorded?

_____Paper AE forms/source documents

__X___Spreadsheet: paper or electronic

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

_X_ Serious/Not serious Required for all protocols

3.4 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___ Subject completes intervention and follow up period of protocol

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/possibley 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	IRB-HSR	Within 7 calendar days from the	Unanticipated Problem report form.

protocol violations This would include a Data Breach.		time the study team received knowledge of the event.	*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, a ITC: if breach involves electronic data- Police if breach includes items that are stolen: Stolen on UVA Grounds OR Stolen off UVa Grounds- contact police department of jurisdiction of last known location of PHI	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

4. **How will the endpoint data be collected/recorded.**

__X___Protocol specific case report forms

_____Source documents

_____Database: Specify Answer/Response:

___✓__Other: Specify Answer/Response: excel spreadsheet with de-identified data from other institutions will be combined with the excel spreadsheets at UVA. The University of Virginia will not be transferring data to other institutions, only receiving data.

5. Data and Safety Oversight Responsibility

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

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

__✓___All site PI's (*for protocols in which there is no common protocol but data from multiple sites will be combined for analysis: Collaborative Site Analysis Studies)*

_____The UVa Cancer Center Data and Safety Monitoring Committee

If your study involves cancer patients, see Question # 6 to help you decide if you should check this option.

_____Medical Monitor

This could include such things as the overall PI of a multisite trial.

_____DSMB/ DSMC

If your study is NIH funded, check with the center to determine if they require a DSMB for this study.
The following groups/individuals are NOT considered a DSMB:
DO NOT CHECK THIS BOX

- Members of the study team
- Medical monitors from a commercial drug company
- Safety review committee within a commercial drug company
- UVa Cancer Center Data and Safety Monitoring Committee
- The overall PI of a multi-site trial or a single individual who may serve as the medical monitor.

The following groups are considered a DSMB:

- A group of scientists, physicians, statisticians and others that are not employees of the commercial drug company that are appointed to oversee the data and safety of subjects in the study.
- A group of scientists, physicians, statisticians and others that are, or are not, employees of UVa, are not affiliated with the UVa study team, and are appointed to oversee the data and safety of the subjects in the study.

DSMB Charter Template
A template for a DSMB charter may be found on the IRB-HSR Website at DSMB Charter Template.

_____Research Monitor: Insert Name Answer/Response: _____

Name required for protocols funded by the Department of Defense

_____Other: Specify Answer/Response:

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

_____Information may be found in the UVa Cancer Center Institutional DSMP
___X__ Collaborative Site Analysis Study- see CSAS section of this DSMP
_____Other- Specify Answer/Response:

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

_____NA- PI is not the overall person overseeing the safety data for this study.
__X___All adverse events
_X___Unanticipated Problems
_X____Protocol violations/Issues of noncompliance
_X____Audit results
_X___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
_____Other: Specify Answer/Response:

5.4 **How often will aggregate review occur?**

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

_____NA- PI is not the overall person overseeing the safety data for this study.
_____Per Enrollment/Events
__X___Annually
_____Semi-Annually
_____Quarterly
_____Monthly
_____Other: Specify Answer/Response:

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

_____NA- PI is not the overall person overseeing the safety data for this study.

_____Per Enrollment/Events

_____Annually

_____Semi-Annually

_____Quarterly

_____Monthly

__X___Other: Specify Answer/Response: N/A no DSMB

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

_____Separate report from DSMB/DSMC or UVa PI

_____Other: Specify Answer/Response:

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?

Decreased infection rates, decreased re-admission to hospital and repeat surgery, decreased time to union, decreased pain and recovery time of patient, decreased morbidity associated with open fractures. The benefits to the society are immense. This avenue of research has the potential to bring down the cost of antibiotic treatment, avoid the negative side effects of the antibiotics such as nephrotoxicity and ototoxicity in people with kidney disease, and improved delivery of drug to the wound site.

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

Yes. The risk-benefit analysis is acceptable.

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8. Cavanaugh DL, Berry J, Yarboro SR et al. Better prophylaxis against surgical site infection with local as well as systemic antibiotics. An in vivo study. J Bone Joint Surg Am 2009;91(8):1907-12.

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: Safeguards for Cognitively Impaired

1. What additional safeguards that will be employed to protect the cognitively impaired subjects?

Use of Surrogate decision-maker when permitted by law, i.e. a legally authorized representative via use of power of attorney/advance directive for research.

2. The following steps will be taken to determine the capacity of a potential subject to give consent for themselves.

A. If there is concern that a potential subject/ subject may be cognitively impaired a determination of incompetence will be made after an evaluation by a person with the appropriate expertise to make such a determination as delegated by the PI. If the subject is a patient in the UVa Medical Center, the Medical Center Policy No. 0024 will also be followed. The determination of competency must be documented in writing.

B. The following methods below will be used to determine capacity for consent:

__X__ Subject is also a patient in the UVa Medical Center and Medical Center Policy No. 0024 will be followed.

___X_ Will rely on individual observation of and interaction with the potential subject as well as the opinion of the medical provider or caregiver, when available. The prospective subject should demonstrate competence in relation to the proposed study in order to be judged capable of providing informed consent for that study. In general, an assessment an individual's capacity to consent will be based on her/his:

- Ability to communicate a choice;
- Ability to understand relevant information;
- Ability to appreciate the nature of the situation and its likely consequences; and,
- Ability to manipulate information rationally (1)

C. An individual will be considered unable to provide consent if he or she has:

- An inability to express or communicate a preference or choice (cannot make up his/her mind, is comatose, or has severe psychotic thought disorders, etc.);
- An inability to understand a situation and its potential consequences as well as the impact of study participation on those circumstances (does not understand that he/she may be hurt or may not be helped or cannot distinguish research from treatment); and/or,
- An inability to provide a logical rationale for participation/no participation in a study (cannot address risk/benefit-related reasons for or against participation in a study.

3. The following steps will be taken to document the determination of competency to consent.

___X__ A note to file will be written and filed in the study files and/or medical records to describe the consenting process. The note will include a description of methods used to determine capacity

of the subject to consent. The note should also include the name of the person determining competency of the subject. May use the SOM CTO form Determination of Capacity to Consent.

4. When will subjects capacity to consent be assessed?

__X___ Prior to initial consenting process if there is a concern that the potential subject has a cognitive impairment. Must be checked for all protocols.

___x__ On a periodic basis throughout the study process if there is a concern that the potential subject has a cognitive impairment. Must be checked if the study is ongoing and there is the possibility that the subject may regain their cognitive ability and be able to consent for themselves.

5. Will UVa researcher conduct the study outside the state of Virginia? NO

6. Are you requesting the use of a Legally Authorized Representative?YES

►IF YES, do you confirm that this study includes none of the following which are conditions which limit the use of an LAR in Virginia?

1. non-therapeutic research unless it is determined by the human research committee (IRB) that such non-therapeutic research will present no more than a minor increase over minimal risk to the human subject.
2. participation in human research on behalf of a prospective subject if the legally authorized representative knows, or upon reasonable inquiry ought to know, that any aspect of the human research protocol is contrary to the religious beliefs or basic values of the prospective subject, whether expressed orally or in writing.
3. participation in human research involving non-therapeutic sterilization, abortion, psychosurgery or admission for research purposes to a facility or hospital as defined by the Code of Virginia at § 37.1-1.
   Answer/Response: YES

APPENDIX: Drug Information

1 What is the drug name, manufacturer and IND# if available?

Tobramycin injectable 80mg/2ml,
Hospira at this time, but subject to change.

2. If IND application has been submitted to the FDA, who is the Principal Investigator on the IND?

SOM CTO review on file-IND exempt

3. What is the phase or stage of this study? Phase 3

APPENDIX: Pharmacy-Investigational Drugs/Biologics

1. What is the name of the investigational drug/biologic?
tobramycin

2. Where will the subjects be seen for the administration/dispensing of the drug?
Inpatient Unit: In the operating room

3. What dose will be utilized in this study?
Trobramycin 80mg/40mL

4. What will be the frequency of dosing in this study?
Once. The second dose that will be given will be the same randomization treatment as the first injection.

5. What will be the duration of dosing in this study?
Once dose administered over 1 minute

6. What route of administration will be utilized?
Injection into a closed wound/subcutaneous tissue

7. Will drug need to be prepared by the UVa Investigational Drug Service (IDS)?
Investigational pharmacy will store the drug and perform the randomization to drug or placebo, and provide the drug to the surgeons on the day of surgery. The randomization code will be stored by the IDS Pharmacy on a spreadsheet.

8. Are there any special handling instructions mandated by the study (e.g. weighing hazardous materials)?
No

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

10. How will missed doses be handled? n/a

11. Will a comparator (active or placebo) be utilized in the protocol? Yes

►**IF YES, comparator is:** Placebo*:* 0.9% Normal Saline injection of 40mL

12. 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

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

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.

Yarboro SR, Baum EJ, Dahners LE. *Locally administered antibiotics for prophylaxis against surgical wound infection. An in vivo study.* J Bone Joint Surg Am. 2008 Feb;90 (2):384.

A 2008 study published by the PI in this study used a rat model, in which they inoculated a surgical wound in the quadriceps muscle with 8.0 x 10(5) colony-forming units of Staphylococcus aureus and then administered one of seven types of treatment: no treatment (control), bacitracin irrigation, calcium sulfate flakes, systemic gentamicin, local aqueous gentamicin, local gentamicin-loaded calcium sulfate flakes, and a combination of local gentamicin-loaded calcium sulfate and systemic gentamicin. The seven treatment groups consisted of ten rats each. To further evaluate a trend, the group treated with systemic gentamicin and the one treated with local gentamicin solution were extended to include twenty-five and twenty-seven rats, respectively. At forty-eight hours postoperatively, specimens from the wounds were obtained for quantitative cultured. They found that the control group, the group treated with bacitracin irrigation, and the one treated with plain calcium sulfate had very high bacterial counts and high mortality rates while the groups treated with gentamicin had low bacterial counts and a 100% survival rate. Local gentamicin was significantly more effective than systemic gentamicin in reducing bacterial counts.

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

From a patient safety standpoint, this drug has been shown to be appropriate for use locally based on cell culture data. The 2mg/ml concentration of aminoglycoside injected into the wounds after closure is high enough to decrease replication of osteoblasts, though not to cause cell death, at sustained concentrations in vitro [4,5]. In vivo, this concentration decreases quickly as it diffuses.

13c. Have there been any human deaths associated with this drug? No

13d. In how many humans has this drug been used previously?

tobramycin is used routinely in patients across the country through a systemic route of administration.

13e. If this protocol will be used in children describe any previous use of this drug with children of a similar age range. None

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

_____ 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;

_____ 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:

tobramycin has long been used in treatment and prophylactic regimens in humans; the dose used in this experiment has been proven on a cellular level in animal models to be non-toxic and effective in prophylaxis against infection.

_X___ 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

_X___ The investigation will be conducted in compliance with the requirements of 21CFR312.7 (Promotion and charging for investigational drugs)

15. Is this a post-marketing study? No

APPENDIX: Recruitment

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

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. ____ 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

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.____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.__X__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.____ 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

e. ____ 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"?** NO

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.

Subjects who are being treated for open fractures at University of Virginia, who agree to participate in the study will be asked to sign an informed consent at the hospital. Subjects will be given ample time to go over the informed consent, and an opportunity will be provided to ask questions. Subjects are also allowed to discuss with family and relatives before they sign the consent. Anywhere, from one hour to one week may pass between written consent and initiation of study procedures.

If subject is unresponsive or intubated, and cannot adequately answer the questions and if it is determined that the patient's level of cognition is not likely to change before surgery, a legally authorized representative (LAR) will be approached for proxy consent. Guidance will be provided to assist the LAR in making consent decision. They will be advised to base the decision on the patient's expressed wishes, or, what they believe the patient would have desired under the circumstances of the injury. His or her beliefs and values. When participant regains capacity to consent during the study period, the participant will be re-consented using standard consenting procedures as described below.

6. **Will subjects sign a consent form for any part of the study?** NO

7. **Will the study procedures be started the same day the subject is recruited for the study?**
   This will depend on the patient's clearance status for the OR. Often, some patients will have to be resuscitated in an ICU setting prior to going to the OR for definitive treatment and wound closure. Also, some wounds cannot be closed during the index procedure and they will have to be taken back to the OR for further treatment and wound closure.

   ►IF YES, explain in detail why the subject cannot be given more time to make a decision to consent.
   Open fractures are surgical emergencies that need to be irrigated/debrided and stabilized and possibly closed as quickly as possible.

   ►IF YES, explain in detail what will be done to assure the potential subject has enough time to make an informed decision.
   The study will be explained to the patient before the patient is brought back to the OR and the patient will have adequate time to ask questions and discuss his or her eligibility in the study with family and friends in the preoperative holding area or in the respective room.

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 that any possible coercion or undue influence is eliminated?

Subjects will be told that their participation is totally voluntary. If they are employees of UVA, they will be assured that their decision to participate or not will not affect their job. If they are students, they will be assured that their decision will not in any way affect their grades.

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

APPENDIX: Privacy Plan for Studies With Consent/HIPAA Authorization

1. Answer the questions below (1A-1G) to describe the plan to protect the data from improper use and disclosure.

1A. Will any HIPPA identifiers be collected by the UVa study team ? YES

INSTRUCTIONS:

Answer YES to any item below that will be written down/kept/recorded in any way.

If you answer NO to all items it means you would never be able to go back and obtain any additional data about an individual.

YES	NO	HIPAA Identifier
	X	1. Name
	X	2. Postal address information, other than town or city, state, and zip code
	X	3. Age or Date of Birth if over the age of 89
	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*)

1A(1)►If you checked any item above, list the HIPAA identifiers that will be kept with the data in the same location (e.g. on the same electronic drive (e.g. F or O drive) or in the same paper file with the data).

INSTRUCTIONS : If you checked # 19 above: If the key to the code (subject # 1= John Smith) will be kept in the same location as the data, list item # 19 below.

Medical Record Number

INSTRUCTIONS:
If you did not list any HIPAA Identifier under 1A(1) skip to 1G.

1B. How will data be collected?

1B(1)._____ Collection of data *ONTO** an individual-use device (e.g. desktop computer, smart phone app, tablet, laptop)

INSTRUCTIONS: *ONTO means the data will reside on the device.
Do not check this box if the device will simply be used to access a server.

If checked answer the following questions:

- What kind of device is it (e.g. laptop, tablet, desktop computer)? _____
- Who manages / supports the device (e.g., Health Systems Computing Services (HS/CS), Information Technology Services (ITS), self)? __

INSTRUCTIONS: If the device is managed/support by *self* you must follow both the setup and maintenance security standards described on the UVa Office of Information Security, Policy & Records Office (ISPRO) webpage: http://www.virginia.edu/informationsecurity/device-requirements.html

- How long with the data remain on the device before it is downloaded to a server _____
- Will anyone other than study team members have access to the data on the device? ___ __
- Will data be downloaded to UVa in an encrypted secure manner such as the use of SFTP or HTTPS? _____
- Are any backups made of the information on the device? _____
- After information is downloaded will you **securely** delete all UVa subject data from the device? _____

  INSTRUCTIONS: For computers not using Windows 8 or newer, download and use the Secure Delete Program from ITS. If using Windows 8 or newer, click on Secure Delete when deleting a file. For Macintosh computers, select "**Secure Empty Trash**" from the Finder menu**.**

- Does the owner of the device (e.g. phone service provider/ app developer) have any rights to use or access the data either individually or in aggregate? _____

1B(2.)_____ Collection of data via web-based format (e.g. online consent, online surveys) via a non-UVa secure server (e.g. NOT HS/CS, ITS or SON SECUREnet)
See 1B(6) below for an exception.

If checked answer the following questions:

- Provide the web address (URL): _____

  INSTRUCTIONS : (e.g., https://name1.name2.org/mystudy/login.html)
  You may locate this URL by taking the following step:
  In Windows under Computer, right click on the Drive. Then click on Properties. The URL name will appear at the very top of the box.
  If you need additional assistance contact your department computer support or system administrator for assistance in answering this question.

- How long will the data remain on the non-UVa secure server before it is downloaded to a server managed by HS/CS, ITS or SON SECUREnet? _____
- Will anyone other than study team members have access to the data on the non-UVa secure server? _____

- Will data be downloaded to a UVa secure server in an encrypted secure manner such as the use of SFTP or HTTPS? _____
  If checked please provide the web address (URL): _____

  INSTRUCTIONS : (e.g., https://name.hsc.virginia.edu)
  You may locate this URL by taking the following step:
  In Windows under Computer, right click on the Drive. Then click on Properties. The URL name will appear at the very top of the box.
  If you need additional assistance contact your department computer support or system administrator for assistance in answering this question.

- Are any backups made of the information on the non-UVa secure server? _____

- After information is downloaded will you **securely** delete all UVa subject data from the Non-UVa secure server? _____

- Do the owners of the non-UVa secure server have any rights to use or access the data either individually or in aggregate? _____

- Is there a Business Associates Agreement (BAA) with the provider of the Non- UVa secure server? _____

1B(3)._____ Directly to a server managed by the principal investigator's department or school
If checked, please provide the name of the server: _____

INSTRUCTIONS : (e.g. name.virginia.edu)
You may locate this URL by taking the following step:
In Windows under Computer, right click on the Drive. Then click on Properties. The URL name will appear at the very top of the box.
If you need additional assistance contact your department computer support or system administrator for assistance in answering this question.

- What kind of individual-use device will be used to connect to this server? (e.g. laptop, tablet, desktop computer)? _____

- Who manages / supports this individual-use device (e.g., Health Systems Computing Services (HS/CS), Information Technology Services (ITS), self)? _____

  INSTRUCTIONS: If the device is managed/support by *self* you must follow both the setup and maintenance security standards described on the UVa Office of Information Security, Policy & Records Office (ISPRO) webpage: http://www.virginia.edu/informationsecurity/device-requirements.html

1B(4)._____ Directly to an Information Technology Services (ITS) managed server.

If checked, please provide the name of the server: _____

INSTRUCTIONS : (e.g., name.its.virginia.edu)
You may locate this URL by taking the following step:
In Windows under Computer, right click on the Drive. Then click on Properties. The URL name will appear at the very top of the box.
If you need additional assistance contact your department computer support or system administrator for assistance in answering this question.

- What kind of individual-use device will be used to connect to this server? (e.g. laptop, tablet, desktop computer)? _____
- Who manages / supports this individual-use device (e.g., Health Systems Computing Services (HS/CS), Information Technology Services (ITS), self)? _____

INSTRUCTIONS: If the device is managed/support by *self* you must follow both the setup and maintenance security standards described on the UVa Office of Information Security, Policy & Records Office (ISPRO) webpage: http://www.virginia.edu/informationsecurity/device-requirements.html

1B(5).__X__ Directly to a Health Systems Computing Services (HS/CS), or School of Nursing SECUREnet with I Key managed server that is configured to store data regulated by HIPAA.
If checked, please provide the name of the server: _central(//hscs-SS10)(F:)___and / or central(\\hscs-share1)(O:)

INSTRUCTIONS : (e.g., \\hscs\name.virginia.edu)
You may locate this URL by taking the following step:
In Windows under Computer, right click on the Drive. Then click on Properties. The URL name will appear at the very top of the box.
If you need additional assistance contact your department computer support or system administrator for assistance in answering this question.

- What kind of individual-use device will be used to connect to this server? (e.g. laptop, tablet, desktop computer)? _Desk top Computer_ ___
- Who manages / supports this individual-use device (e.g., Health Systems Computing Services (HS/CS), Information Technology Services (ITS), self)? __HS/CS___

INSTRUCTIONS: If the device is managed/support by *self* you must follow both the setup and maintenance security standards described on the UVa Office of Information Security, Policy & Records Office (ISPRO) webpage: http://www.virginia.edu/informationsecurity/device-requirements.html

1B(6)._____ Directly to a server managed by the sponsor or CRO in which the data will be sent and stored in an encrypted fashion (e.g. must be shared and stored via Secure FX, Secure FTP, HTTPS, PGP) and the server is configured to store data regulated by HIPAA.

- What kind of individual-use device will be used to connect to this server? (e.g. laptop, tablet, desktop computer)? __ ___

- Who manages / supports this individual-use device (e.g., Health Systems Computing Services (HS/CS), Information Technology Services (ITS), self)? _____

INSTRUCTIONS: If the device is managed/support by *self* you must follow both the setup and maintenance security standards described on the UVa Office of Information Security, Policy & Records Office (ISPRO) webpage: http://www.virginia.edu/informationsecurity/device-requirements.html

1.B(7).__x___ Paper

►IMPORTANT: If you checked any of the items 1B(1) through 1B(4) submit ISPRO approval with new protocol submission.

You should consult with ISPRO during the development phase of this protocol if your protocol will involve highly technical issues such as the creation of a website to collect data, software application development, the use of a smart phone app, or if you plan to store identifiable data ONTO a tablet/laptop.

Otherwise submit the protocol to ISPRO for review when it is submitted to the IRB-HSR for pre-review.

ISPRO CONTACT INFORMATION:
UVa Office of Information Security, Policy & Records Office (ISPRO)
www.virginia.edu/ispro
Email: IT-Security@Virginia.edu

1C. How will data be stored by the UVa study team?

___X__ Data, which may include health information or other highly sensitive data, will be stored with HIPAA identifiers.

1D. Will any of the data be stored electronically by the UVa study team?YES

1D(1)►IF YES, will it include storage of any health information or other sensitive data? YES

1D(2)►IF YES, will you store/keep any of the HIPAA identifiers listed below in electronic format? ANSWER QUESTION IN TABLE BELOW

YES	NO	HIPAA Identifier
	X	1. Name
	X	2. Postal address information, other than town or city, state, and zip code
	X	3. Age or Date of Birth if over the age of 89
	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*)

1D(3)►If you checked any item above, list the HIPAA identifiers that will be kept with the data in the same location (e.g. on the same electronic drive (e.g. F or O drive) or in the same paper file with the data).
Medical Record Number

1D(4) Check all locations where the data with these HIPAA identifiers will be kept :

__X___ in an electronic file- *If checked list HIPAA identifiers:_MRN____*

1E. If you listed any HIPAA identifier under 1D(3), where will the data be stored?

1E(1)_____ a server managed by the principal investigator's department or school that is configured to store data regulated by HIPAA or highly sensitive data.

- If checked, please provide the name of the server: _____
- Contact information for the person(s) who manages / supports this server. _____

SKIP the following two questions if you checked 1B(3)

- What kind of individual-use device will be used to connect to this server? (e.g. laptop, tablet, desktop computer)? _____

- Who manages / supports this individual-use device (e.g., Health Systems Computing Services (HS/CS), Information Technology Services (ITS), self)? _____

1E(2)_____ a Information Technology Services (ITS) managed server that is configured to store data regulated by HIPAA

- If checked, please provide the name of the server: _____

INSTRUCTIONS : (e.g., name.its.virginia.edu)
You may locate this URL by taking the following step:
In Windows under Computer, right click on the Drive. Then click on Properties. The URL name will appear at the very top of the box.
If you need additional assistance contact your department computer support or system administrator for assistance in answering this question.

SKIP the following two questions if you checked 1B(4)

- What kind of individual-use device will be used to connect to this server? (e.g. laptop, tablet, desktop computer)? _____

- Who manages / supports this individual-use device (e.g., Health Systems Computing Services (HS/CS), Information Technology Services (ITS), self)? _____

INSTRUCTIONS: If the device is managed/support by *self* you must follow both the setup and maintenance security standards described on the UVa Office of Information Security, Policy & Records Office (ISPRO) webpage: http://www.virginia.edu/informationsecurity/device-requirements.html

-

1E(3)__X___ a Health Systems Computing Services (HS/CS) managed server that is configured to store data regulated by HIPAA.

- If checked, please provide the name of the server: _ central(//hscs-SS10)(F:) and / or central(\\hscs-share1)(O:)___ ____

1E(4)_____ a server managed by the sponsor or CRO in which the data will be sent and stored in an encrypted fashion (e.g. must be shared and stored via Secure FX, Secure FTP, HTTPS, PGP) onto a server that is configured to store data regulated by HIPAA.

INSTRUCTIONS: The study team should confirm the security of the site with the sponsor, CRO or other outside group.
NOT ALLOWED if you have answered YES to any HIPAA identifier above and data will not be sent/stored in an encrypted manner.

►IMPORTANT: If you checked any of the items 1E(1) or 1E(2) submit ISPRO approval with new protocol submission. N/A

You should consult with ISPRO during the development phase of this protocol if your protocol will involve highly technical issues such as the creation of a website to collect data, software application development, the use of a smart phone app, or if you plan to store identifiable data ONTO a tablet/laptop.

Otherwise submit the protocol to ISPRO for review when it is submitted to the IRB-HSR for pre-review.

ISPRO CONTACT INFORMATION:
UVa Office of Information Security, Policy & Records Office (ISPRO)
www.virginia.edu/ispro
Email: IT-Security@Virginia.edu

1F. Will any of the data be collected or stored in hard copy format by the UVa study team (*e.g. on paper*)? NO

1G. The following procedures must also be followed.

- Only investigators for this study and clinicians caring for the patient will have access to the 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 Universities Requirements for Securing Electronic Devices.
- If identifiable health information is taken away from the UVa Health System, Medical Center Policy # 0218 will be followed.
- The data will be securely removed from the server, additional computer(s), and electronic media according to the University's Electronic Data Removal Policy.
- The 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 .
- The 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
-health information that reveals an individual's health condition and/or history of health services use.
Protected Health Information (PHI) a type of Highly Sensitive Data, is health information combined with a HIPAA identifier
Identifiable Health Information 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.* See Table A below for details.

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 servers 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)**
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: 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	Must report in accordance with protocol/ in accordance with the Information Security Incident Reporting Policy

** 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.*

2. Will specimens be stored at UVa by the UVa study team?NO

3. **Do you confirm that you will not reuse the identifiable data (HIPAA identifiers or health information) or disclose any of this information to any other person or entity except as outlined in this protocol, except as required by law, for authorized oversight of the research study, or use it for other research unless approved by the IRB-HSR? Yes**

This means that after the study is closed at UVa:

- You cannot contact the subject by any method (you cannot call them, send a letter, talk to them in person about the study, etc) without additional IRB approval
- You cannot use the data for any research that is not already described in your IRB protocol without additional IRB approval (if you change your hypothesis you must modify your protocol)
- You cannot share your research data with another researcher outside of your study team without additional IRB approval
- Any health information with HIPAA identifiers will be shredded or discarded by using recycling bins for confidential material found in clinic settings. For large item disposal of confidential material contact Environmental Services at 2-4976 or University Recycling at 2-5050.

TABLE A: HIPAA Identifiers (Limited Data Set)

1. Name
2. Postal address information, other than town or city, state, and zip code
3. Telephone numbers
4 Fax numbers
5. Electronic mail addresses
6. Social Security number
7. Medical Record number
8. Health plan beneficiary numbers
9. Account numbers
10. Certificate/license numbers
11. Vehicle identifiers and serial numbers, including license plate numbers
12. Device identifiers and serial numbers
13. Web Universal Resource Locators (URLs)
14. Internet Protocol (IP) address numbers
15. Biometric identifiers, including finger and voice prints
16. Full face photographic images and any comparable images
17. 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.)

The Pharmacy department is assisting us with this project, they will be storing the data of which patient's receive the experimental or control treatment. They will be storing the data on a Health Systems Computing Services managed server (hospital based) that is configured to store data regulated by HIPAA. Once we have gathered enough patient's to they will release the data to us to analyze.