Original Protocol and Amendments

March 8, 2018 - May 29, 2018

NCT04821245

ID: BRI IRB18-008

Defining Normal Postoperative Magnetic Resonance Imaging after Total Knee Arthroplasty

Protocol Title: Defining Normal Postoperative Magnetic Resonance Imaging after Total Knee Arthroplasty

Date Submitted:

Approval Period: Draft

Important Note: This Print View may not reflect all comments and contingencies for approval. Please check the comments section of the online protocol. Questions that appear to not have been answered may not have been required for this submission. Please see the system application for more details.

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* * * Personnel Information * * *

Click "Help" (upper right corner of screen) for guidance regarding who to include below (Key Personnel) and what CITI Training is needed. See the Clinical Research Glossary for definitions. Questions: Contact the Research Protections Department

Principal Investigator

Client defines "Investigator" as an individual who conducts a research study. If the study is conducted by a team of individuals, the Investigator is the responsible leader of the team.

Name of Principal Investigator*		Degree (MD/PhD/BSN/etc.)		Title
Neal, Joseph		MD		ANESTHESIOLOGIST
Email*		**Phone**		**Fax**
Joseph.Neal@virginiamason.org		206-223-6980		
VM/BRI Department		**Investigator Affiliation Check ALL that apply***		**Mailstop**
Anesthesiology	X	VM personnel		B2-AN
		BRI personnel		Zip code
		Other		98101
Training Details				
No training data is available.				

Sub-Investigator(s)

Sub-Investigator	Degree (MD/PhD/BSN/etc.)	Title	Research Department
Blackmore, Craig	MD	RADIOLOGIST	Radiology MD Admin
Verdin, Peter	MD	ORTHOPEDIC SURGEON	Orthopedics - Outpatient

Sub-Investigator(s)

Name of Sub-Investigator(s)	Degree (MD/PhD/BSN/etc.)	Title
Blackmore, Craig	MD	RADIOLOGIST
Email*	**Phone**	**Fax**
Craig.Blackmore@virginiamason.org	206-223-6851	
VM/BRI Department	**Investigator Affiliation Check ALL that apply***	**Mailstop**
Radiology MD Admin	X VM personnel	R3-324
	BRI personnel	**Zip code**
	Other	98101
Role in Study	Radiologist	

Training Details
No training data is available.

Sub-Investigator(s)

Name of Sub-Investigator(s)	Degree (MD/PhD/BSN/etc.)	Title
Verdin, Peter	MD	ORTHOPEDIC SURGEON
Email*	**Phone**	**Fax**
Peter.Verdin@virginiamason.org	206-223-7530	X6-ORT
VM/BRI Department	**Investigator Affiliation Check ALL that apply***	**Mailstop**
Orthopedics - Outpatient	X VM personnel	
	BRI personnel	**Zip code**
	Other	98101

Role in Study

Training Details			
Course	**UserID**	**CourseCompletionDate**	**CourseExpirationDate**
CITI Good Clinical Practice	peter.verdin	11/14/2016 3:34:28 PM	11/14/2019 3:34:28 PM

Study Coordinator

Study Coordinator	Degree (MD/PhD/BSN/etc.)	Title	Research Department
Neal, Joseph	MD	ANESTHESIOLOGIST	Anesthesiology

Study Coordinator

Name of Study Coordinator	Degree (MD/PhD/BSN/etc.)	Title
Neal, Joseph	MD	ANESTHESIOLOGIST
Email*	**Phone**	**Fax**
Joseph.Neal@virginiamason.org	206-223-8822	
VM/BRI Department	**Investigator AffiliationCheck ALL that apply***	**Mailstop**
Anesthesiology	X VM personnel	B2-AN
	BRI personnel	**Zip code**
	Other	98101

Training Details
No training data is available.

Regulatory Contact (Primary IRB contact if not PI or Study Coordinator)

Name of Regulatory Contact		Degree (MD/PhD/BSN/etc.)	Title
Email*		**Phone**	**Fax**

VM/BRI Department	Investigator Affiliation Check ALL that apply*		Mailstop
		VM personnel	
		BRI personnel	Zip code
		Other	
Training Details			
No training data is available.			

Additional Personnel Information: (Use the area below if necessary to provide additional information regarding the personnel on this protocol)

Dr. Lauren Steffel, Puget Sound VA Health Services, will participate in manuscript writing and data analysis. She will have no contact with Virginia Mason subjects. The data that she will have access to will be de-identified with regard to subject PHI.

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* * * Subject Checklist * * *

Subject Checklist

Select all that apply:

Retrospective medical records (e.g. Chart Review)

Tissue, blood, other specimens (e.g. repository)

X Individuals with underlying medical conditions

X Healthy individuals

Select all vulnerable groups:

Check all targeted or possibly included subjects. This also applies to retrospective chart reviews.
Some groups (e.g. prisoners, pregnant women, or children) may require additional IRB oversight per federal regulations.

Prisoners

45CFR46 Subpart C (Should be excluded unless you know subject(s) will be "in prison" at the time of enrollment. Notify IRB immediately if a subject becomes incarcerated after enrollment. This population can not be reviewed exempt.)

Pregnant women

45CFR46 Subpart B

Females of childbearing potential

Children (under 18)

45CFR46 Subpart D

Persons incompetent to give consent (e.g., dementia, comatose, have legally authorized representative)

Economically/educationally disadvantaged.

Illiterate

Non-English speaking

See: VM Interpreter Services

Are any other subjects outside of the above targeted or possibly included in this study? N

If yes, describe below:

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* * * Study Location * * *

Study Location

1. Click "add" and create a separate row in the table below for each unique VM / BRI study location.

VM/BRI Table

VM Location	Other VM Location:	VM location Study Activities	Other Activities
Main Campus Seattle - Clinic / Hospital		Blood draw, Informed consent discussion, Ongoing study visits, Screening visits, Specific procedures associated with the study	

VM/BRI Table

Location Main Campus Seattle - Clinic / Hospital

Activity Blood draw,Informed consent discussion,Ongoing study visits,Screening visits,Specific procedures associated with the study

2) Are there any locations outside of VM / BRI that are involved in any way with this study? If yes, explain below. If no, proceed to the next section. N

i. Are any outside locations "engaged"with this research study? If yes, explain: (click on "Help" for more information regarding engagement) N

ii. Will the BRI IRB be responsible for oversight (IRB of Record) for any study procedures conducted at outside locations? If yes, describe in the table below (click "add"). If no, confirm who is the IRB of Record for engaged activities outside of VM in the space below and then proceed to the next section. N

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* * * General Checklist * * *

General Checklist

Select All That Apply: At least 1 box must be checked to proceed. If none are applicable contact the IRB at IRB@benaroyaresearch.org Use the attachment section to add separate documents or forms.

X Protected Health Information (PHI) will be viewed, created, accessed, used, or disclosed by VM/BRI personnel or others. (Checking this box activates the HIPAA section)

Questionnaire/Survey

Tissues or data to be stored for future research projects (e.g. registry or repository)

Tissues or data to be sent out of VM / BRI as part of a research agreement - Material Transfer Agreement (MTA)- Data Use Agreement (DUA)

X FDA regulated device (Investigational or otherwise)- This includes Humanitarian Use Devices (HUD)

FDA regulated drugs, reagents, or chemicals (Investigational or otherwise)

This study is or will be posted on ClinicalTrials.gov

If checked, specify number:

Radioisotopes/radiation-producing machines, even if standard of care (Radiation Safety)

VM/BRI Institutional Biosafety Committee (IBC) Review Required- Clinical research involving recombinant and/or synthetic nucleic acid

Request to Rely on Another IRB - Please upload completed Request to Rely and associated documents in attachment section (This applies for Cooperative Review studies.)

IRB Authorization Agreement (IAA), Memorandum Of Understanding (MOU), etc.(attach in the Attachments section (This only applies to studies where the Client IRB is the "Reviewing" IRB).

X A stand-alone protocol already exists.

Checking this box doesn't reduce the number of questions you need to answer. However, you can be brief with your answers and include references to the stand-alone protocol (e.g. section, page #) for more information. Use the attachment section to include the stand-alone protocol with your submission.

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* * * Funding * * *

Funding / Resources

1) Is there funding or other resources required for this project? Y

No means absolutely no internal or external funds, services, skills, or products (e.g., statistical services, database warehousing, free test article) are provided. If no, proceed to the next section.

If yes, Click "add" and create a separate row in the table below for each unique funding source.

Funding / Resources Table

Funding Name	BRI Funding #	Restricted BRI Funds	Unrestricted BRI Funds	Federal Grant	Federal Funding #, Grant #	Non-Profit Foundation	Industry Funding
Washington State Society of Anesthesiologists Seafair Grant Award	Through VM Foundation	N	N	N		Y	N

Funding / Resources Table

Name of Funding Entity	Washington State Society of Anesthesiologists Seafair Grant Award
BRI Funding Number	Through VM Foundation
BRI restricted funds?	N
BRI unrestricted funds?	N
Federal Grant funds?	N
Non-Profit Foundation?	Y
Industry Funding	N

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* * * Application Type Checklist * * *

Please check one of the boxes below to determine how to move forward with your project. The US Office of Human Research Protections (OHRP) has created graphic aids to help with deciding if your research requires IRB oversight. In addition, please contact the BRI Research Protections Department with questions.

Application type checklist

Not Human Subjects Research (This form is not currently available through eProtocol. Please click "https://www.benaroyaresearch.org/sites/default/files/Human%20Subjects%20Determination%20Form.doc" target=_blankhere if applicable.)

Exempt

X Expedited/Full Board (This includes Cooperative and Chart Reviews.)

Indicate what level of review you anticipate for this protocol:

Full Board (greater than minimal risk)

X Expedited (minimal risk)

"https://www.benaroyaresearch.org/our-research/clinical-research/for-investigators/starting-study/cooperative-trials" target=_blankCooperative (approval by another IRB of record, regardless of risk level)

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* * * Expedited Paragraphs * * *

EXPEDITED REVIEW CATEGORIES If this is a FULL BOARD study, or COOPERATIVE (IRB of Record is not BRI), then proceed to next section.

For expedited review all aspects of the research must be: (1) Minimal Risk (2) Involve one or more categories listed below. Select all that apply (Click Help for more information):

1. Clinical studies of drugs and medical devices only when condition (a) and (b) are met.

   a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

   b) Research on medical devices for which

      i) An investigational device exemption application (21 CFR Part 812) is not required; or

      ii) The medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

X 2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

   a) From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the

amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

b) From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by non-invasive means.

Examples:

a) Hair and nail clippings in a non-disfiguring manner.

b) Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction.

c) Permanent teeth if routine patient care indicates a need for extraction.

d) Excreta and external secretions (including sweat).

e) Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue.

f) Placenta removed at delivery.

g) Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor.

h) Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.

i) Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings.

j) Sputum collected after saline mist nebulization.

X 4. Collection of data through non-invasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples:

a) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy.

b) Weighing or testing sensory acuity.

c) Magnetic resonance imaging.

d) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography.

e) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

X 5. Research involving materials (data, documents, records, or specimen) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (NOTE: Some research in this paragraph may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

6. Collection of data from voice, video, digital, or image recordings made for research purposes.

7. Research on individual or group characteristics or behavior (including, but not limited to, research on

perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects - 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

* * * Summary, Purpose, Procedures * * *

BRI Study ID Number - From the Clinical Research Program (e.g. CRP170XX)

CRP18023

Unit / Department - Administrative Oversight of Research

Defining Normal Postoperative Magnetic Resonance Imaging after Total Knee Arthroplasty

1. Summary

Provide a summary of the scope of work of this protocol.

Recent reports(1) describe sentinel cases of presumed local anesthetic-induced myotoxicity occurring after continuous adductor canal blocks (CACB) that were placed to provide analgesia after total knee arthroplasty (TKA). Crucial to the diagnosis, management, and eventual understanding of this newly described anesthetic complication is elucidating what constitutes normal postoperative magnetic resonance imaging (MRI) after TKA. A recent retrospective review of MRIs obtained for various indications within a week of TKA failed to identify a consistent pattern of MR findings that might have defined "normal MRI imaging" after TKA (BRI 16092, Magnetic Resonance Imaging of the Quadriceps Muscle After Total Knee Arthroplasty). The logical next step in this investigation would be to obtain MRIs in TKR patients just prior to hospital discharge after an otherwise normal postoperative course.

2. Purpose

Describe the purpose for the proposed project as well as the hypotheses/research questions to be examined.

This knowledge is crucial for proper diagnosis and further understanding of this sentinel complication.

3. Procedures

a) Describe the activities/procedures to be conducted in chronological order (e.g. pull charts/data from Cerner, screening, interventions/interactions with subjects, data collection, photographing, audio and video recording, follow-up.)

-Patients of various age and sex that are scheduled for unilateral TKR will be approached by VM orthopedic surgeons to ascertain their willingness to volunteer for this study
-Identified patients will be consented for study participation by the PI at least 24 hours prior to their entry into the study
-All patients will undergo the standard VMMC TKA clinical pathway, which includes a 2 day continuous adductor canal block
-If their postoperative course has been normal, 10 volunteers will undergo unilateral thigh MRI prior to discharge home on the morning of postoperative day 2. These patients will have pre- and post-op CPK and aldolase levels analyzed.
-Leg MRIs will be graded using a standardized checklist by a supervised radiology resident who is unaware of the study's purpose.

b) Explain who will conduct the procedures. Include where and when they will take place.

-MRIs will be obtained as scheduled cases at VMMC
-CPK and aldolase will be obtained and analyzed by VMMC laboratory
- by a radiologist who is unaware of the study's purpose

c) Will you be conducting procedures directly with patients? If yes, answer the questions below. If no (e.g. chart review only), proceed to question 4.0 Study Duration. Y

i) Are there any procedures considered experimental and outside standard of care or established practices at Virginia Mason, including follow-up procedures? Y

If yes, explain.

Lower extremity MRIs are standard, but are not a routine part of postoperative TKA care. CPK and aldolase analyses before and after TKA is non-standard.

ii) Will blinding be involved with this study? Y

If yes, explain.

-The interpreting radiologist will be blinded as to the study's purpose

iii) Will deception be used? N

If yes, provide a rationale and describe debriefing procedures. Submit a debriefing script in attachments section.

iv) Will audio, photographs, or video taping of individuals occur? N

If yes, describe and clarify what will become of the tapes/photographs (e.g., shown at scientific meetings, erased, etc.).

4. Study Duration

What is the anticipated start date and duration of the proposed study?

We plan to start immediately after IRB approval. We anticipate all 20 volunteers should be recruited and studied within a 3 month period

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* * * Background and additional procedures * * *

5. Background and additional procedures

a. Relevant Background: Discuss the present knowledge, appropriate literature and rationale for conducting the research.

Local anesthetics consistently induce myotoxicity in animal models and in up to 0.5% of humans after ophthalmic blocks, yet clinically apparent myotoxicity in patients undergoing peripheral nerve blocks was heretofore believed to be nearly non-existent.(2) This changed after introduction of continuous adductor canal blocks (ACB) at Virginia Mason Medical Center when 4 patients developed symptoms, MRI findings, and neurophysiologic testing compatible with local anesthetic-induced myotoxicity. In short order, other cases were reported from the Swedish Orthopedic Institute, 3 from retrospective analysis of other post-TKA MRIs obtained at Virginia Mason, and anecdotally from practices throughout the United States. These sentinel complications have resulted in major morbidity for the affected patients. After a normal early postoperative course, the patients rapidly developed flaccid quadriceps muscles and the inability to lift the operative lower extremity against gravity, with consequent halting of their rehabilitative trajectory. While fortunate patients recovered fully or nearly so after weeks to a few months as the unaffected myoblasts regenerated, less fortunate patients have never recovered to baseline.

Because non-ophthalmic myotoxicity has never been described to this degree in humans, little is known about its etiology, diagnosis, and treatment. Definitive diagnosis of myositis requires muscle biopsy, but this invasive and expensive intervention is unlikely to occur. All patients in our series had MRI signals consistent with edema and inflammation, consistent with myositis. However, the radiologic literature is silent with regard to what constitutes normal MRI findings immediately after TKA. Therefore, the MRI pathology that we observed, while clearly demonstrating inflammatory changes in the anterior compartment of the leg, could conceivably represent normal postoperative findings. We have attempted to study this question by retrospectively reviewing MRIs of patients who underwent leg MRI within a week of TKA. While we could identify several patients with clinical presentations consistent with undiagnosed myotoxicity, we were unable to confidently discern pathological findings versus 'normal' postoperative changes on imaging.

b. If applicable, please describe statistical methods of the research and plans for analysis of the data (i.e. planned statistics, justification of sample size, etc.).

Observational convenience sample, therefore N/A

c. Are there any alternative treatments to participating in this research (e.g., standard of care treatment, etc.)? N

If yes, describe. Any standard treatment that is being withheld must be disclosed. This information must be included in the consent form.

d. Can subjects receive alternative treatment outside of enrolling in this study? N/A

e. Will subjects be followed after their participation is complete? N

If yes, explain why and describe how:

f. Is this a cooperative study (e.g. UW, FHCRC is IRB of record)? N

(If yes, answer the questions below. If no, proceed to the next section. Click here for more information.)

i. Has this study been approved by the IRB of record? (NOTE: BRI IRB cannot review any COOP study not currently approved by the IRB of record)

If yes, when did the initial approval for this study occur?

ii. Has this study undergone Continuing Review (CR) at the IRB of record?

If yes, what are the current approval dates?

iii. Will there be any costs to VM for study procedures (e.g. lab costs, etc.)?

If yes, how will these costs be paid to VM? (e.g., direct billing to your grant, etc.)

iv. Will potential subjects from VM be approached?

(Note: Refer to Non-VM Investigator Patient Approach Procedures for the correct procedures.)

If yes, describe how subjects will be approached and by whom.

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* * * Subject Population * * *

6. Subject Population

a) Complete the projected subject enrollment information below:List multiple subject groups/cohorts as appropriate.(e.g. retrospective, prospective, children, adult, controls, treatment, etc.)

Subject Enrollment

Subject Group (DEFINE: cases/controls/records/ specimens etc.)	Age Range	Expected Number at End of Study (locally)	Expected Number at End of Study (Total if multi-site)	Expected Enrollment next 12 months
20	50-75	20		20

b) Complete the vulnerable subject table below:

Potentially Vulnerable Subject Populations

	Targeted	Possible Inclusion	Excluded	N/A
Prisoners: FAQ (Note: should be excluded unless you know subjects will be "in prison" at the time of enrollment. Notify IRB immediately if a subject becomes incarcerated after enrollment.)			X	
Pregnant Women: (45CFR Subpart B)			X	
Children (under 18): 45CFR46 Subpart D			X	
People not competent to provide informed consent			X	
If the above populations are targeted or possibly included, explain: (Give rationale and specific steps to protect those populations)				
Female of childbearing potential:			X	
If excluded, explain:				
Non-English Speaking: VM Interpreter Services			X	
If Non-English Speaking subjects are targeted or possibly included, give rationale and specific steps to protect those populations. If excluded, explain.	Concern regarding not fully understanding through the translator that this study involves the acquisition of MRI and enzyme tests that are not part of a standard knee replacement hospitalization			
New Description	New Description	New Description	New Description	New Description
New Description	New Description	New Description	New Description	

c) Are any other potentially vulnerable subjects (sight impaired, illiterate, etc.) targeted or possibly included in this study? If yes, explain and provide steps to protect this population: N

d) Inclusion and Exclusion Criteria (e.g., Participants must have 20/20 vision, Participants must be 30-45 years of age, etc.)

i. Identify inclusion criteria.

-Anticipated unilateral TKA performed under the standard VMMC joint pathway, with 2 night stay postop
-Subjects will be operated by a single surgeon (Dr. Verdin) to eliminate possible confounders related to surgical technique
-Subjects must be willing to volunteer for MRI study and CPK and aldolase blood draws

ii. Identify exclusion criteria.

-Any contraindication to use of spinal anesthesia or adductor canal-based analgesia
-History of muscle wasting or related disease
-History of auto-immune disorders that may affect the musculature
-History of pre-existing neurologic condition affecting the lower extremities
-Allergy to radiologic contrast
-Contraindications to MRI exam

e) To provide support for your projected enrollment goals, how many patients at VMMC do you anticipate would have met your eligibility criteria over the last 1-5 years? If NA or no numbers available, explain why and provide rationale to support your projections:

1000 per year

f) How long do you anticipate it will take to complete accrual for this study?

3 months

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* * * Recruitment Process, Subject Compensation and Costs * * *

7. Recruitment Process:

a) Describe the step-by-step procedures for identifying and recruiting potential research subjects and/or requesting their data or specimens.

-Patients of various age and sex that are scheduled for unilateral TKA will be approached by Dr. Verdin to ascertain their willingness to volunteer for this study
-Identified patients will be consented for study participation by the PI (Dr. Neal) at least 24 hours prior to their surgery

b) Identify who will contact prospective subjects. (complete request for waiver of consent if applicable)

Joseph M. Neal, MD

c) Planned Subject Identification Methods:

VM Medical Records / Chart Review	Direct Advertising
From PI's own practice / department Records	Referrals
Specific registries, specify IRB#:	
Outside Institution, please specify:	

X Other, explain below:

From VMMC orthopedic surgical patients scheduled for TKA. Initial willingness to participate in the study will be ascertained by Dr. Verdin or his physician assistant.

d) Planned Recruitment Materials / Methods:

X Face to face interactions	Flyers / posters
Phone Scripts	Letters to providers / schools / organizations
Television ads	Newspaper ads
Letters to prospective subjects	Radio ads
Oral Scripts	PowerPoint presentations
Internet ads / postings	Email
X Other, please specify:	Phone conversation with PI

NA

Attach ALL recruitment information in its final form using the Attachments section of this IRB eProtocol form.

See BRI IRB Recruitment Material Guidance.

8. Subject Compensation and Costs:

a) Will subjects or their health care providers be required to pay for any study related procedures or products? N

i. If "Yes," explain. Max out of pocket? Are any funds available from the study if the subjects insurance will not cover study-related procedures or products?

b) Will subjects receive compensation in any manner for participation? If "Yes," complete the questions below. If "No", skip to the next section. N

i. Will subjects receive monetary payment? If yes, describe payment schedule including per visit and total.

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ii. Will any one payment be more than 40% of total compensation? If "Yes," explain and provide rationale.

iii. Will other forms of compensation be provided? If yes, describe below.

Parking Voucher	Gifts
Transportation	Lodging
Gift card/certificate	Other (describe below)

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* * * Risks * * *

9. Risks / Data Safety Oversight / Monitoring

(Click "Help" above for more information)

a) PI's evaluation of the overall level of Risk. (Please check one: minimal, or greater than minimal.) Minimal risk: The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life, or during the performance of routine physical or psychological examinations or tests.

X Minimal risk

Greater than minimal risk

b) Check all potential risks/side effects to subjects. Check only added potential risks/side effects that may occur to subjects from the research and not those that would occur if subjects were to receive standard treatment/procedures only. [Note: Virtually all research studies involve "breach of confidentiality" and "invasion of privacy" as potential risks since several entities may have access to research records (e.g., FDA, NIH, IRB, etc.). Risks must be consistent with the consent form and protocol.]

Risk / Side Effects

Physical Harms		Psychological		Social Economical	
	Minor Pain		Depression	X	Breach of Confidentiality, resulting in:
	Discomfort		Confusion	X	Invasion of privacy
	Serious Injury		Hallucination		Potential loss of employment or insurability
	Death		Stress		Potential criminal prosecution
	Injury from invasive medical procedure		Guilt		
	Harm from possible side effects from drugs		Loss of self-esteem		None (only applicable if all data is stripped of all identifiers and not coded)
X	Rare allergic reaction to radiologic contrast dye		Embarrassment		
	None	X	Possible anxiety or claustrophobia during MRI exam		
			None		

c) Describe the procedures or safeguards in place to protect against or minimize potential risks (e.g., referral to psychological counseling resources).

-Standard assessment of allergy or MRI-associated risk prior to MRI study

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-Standard care during phlebotomy
-Referral to psychological counseling if indicated

d) Who will be monitoring the risks noted above to ensure the safety of subjects?

X The Principal Investigator Describe your monitoring plan for reviewing interim results and/or safety concerns during the study:

-Contact with the volunteer prior to obtaining the MRI
-Post-procedural contact (after MRI and blood draw) to ascertain any concerns
-Contact information of PI will be made available to the volunteers

A group representing the study sponsor State name of group and describe monitoring plan for reviewing interim results and/or safety concerns during the study:

A Data Safety Monitoring Board (DSMB) State name of DSMB and describe procedures for submitting summary reports from the DSMB to the IRB:

Other:

If multi-site trial, are DSMB report(s) available for research already conducted?If yes, attach DSMB reports. (see clinical research glossary for "DSMB" clarification. If you think your study warrants DSMB oversight and you do not know of one to utilize, please contact the IRB office.)

e) Are there any stopping rules based on the risks noted above, or other study criteria? If yes, describe below and include study endpoints. (Click "Help" above for more information.)/ N

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* * * Benefits * * *

10. Benefits(This section is not enabled for exempt or cooperative studies)/

a) Are there any direct benefits to the research participants? Note: Direct benefit is a valued or desired outcome; an advantage (please do not include monetary inducement or compensation).If yes, please describe. N

b) Are there any anticipated benefits of this study to society, academic knowledge or both? If yes, please describe. Y

The results of this study should define the effectiveness of MRI and/or CPK / aldolase as diagnostic tools in future patients with suspected local anesthetic-induced myotoxicity

c) Explain how the potential benefits justify the potential risks involved in participation in this research.

For this previously unknown complication, new knowledge is critical for both understanding the proper diagnosis and for complication management. We have tried other routes to understand the diagnostic paradigm, to no avail. The low risk and inconvenience of postoperative MRI and CPK / aldolase studies will facilitate further knowledge related to this previously unknown complication.

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* * * Confidentiality * * *

11. Confidentiality

a) Which of the following types of data will be associated with this study. Consider all aspects of the study.(Click 'Help" above for more information)/

X Identifiable
Anonymous
X De-identified
Coded

b) Describe your protection method(s) in two or three sentences (e.g. coding system, limited access, password protected, certificate of confidentiality, etc.). Include safeguards to protect against direct or indirect identification of subjects in any reporting of research results (e.g. publications):

-MRIs contain patient names and medical record numbers will be seen by the blinded radiologist
-CPK reports contain patient names and medical record numbers, but will be seen only by Dr. Neal and the patient's orthopedic team
-A password-protected spreadsheet housed on a VMMC password-protected computer will be used to link MRN to radiologist-generated MRI standard reading and CPK levels
-MRNs will be removed from the spreadsheet prior to sharing with Dr. Steffel (at VA Puget Sound).
-Subject number, age, results of MRI and enzyme analysis, sex. No other identifiable information

c) Other than study staff and BRI Regulatory & Compliance, what entities will have access to research records and/or data that identify subjects (including coded data)?

NIH	Study Sponsor	Contracted monitor
FDA	Personal physician	X None

Other: (explain below)

d) How will research data be recorded?

Case report forms	Remote data entry (e.g. central database off site)	X Local database (e.g. Excel spreadsheet)
REDCap database	Patient medical records	N/A

Other: (explain below)

e) How will research records be stored locally?

X VMMC/BRI server	X Investigator's computer	Locked file cabinet
Locked office	N/A	Other: (explain below)

f) How will specimens be stored?

Limited access refrigerator / freezer	Locked cabinet / office
X N/A	Other: (explain below)

g) After completion of this study, will you keep any data and/or specimens for future research purposes? N

if yes then answer the following questions:Describe why the information and/or specimens will be retained (i.e., possible use for another research project[s], etc.). Note: Separate IRB applications must be submitted for additional use of retained data and/or specimens outside the approved protocol:

Describe in two or three sentences how the confidentiality of the retained information and/or specimens (whether directly identifiable or coded) will be maintained:

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h) Indicate the length of time research records and/or specimens will be kept before EITHER all identifiers/codes are removed OR the records and/or specimens are destroyed. Describe the procedures you will use.

Research records will be kept 1 year after publication of our results. After that, the spreadsheet will be turned over to BRI for archiving.

---

* * * Consent Information * * *

12. Consent Information

Consent Instructions and Checklist

Template Consent Forms and Guidance

a) Click "Add" to enter information in the "Informed Consent" table below. This includes translated consents and waivers of consent. Exempt Studies: This table is disabled. If a consent is used then attach in the attachment section. Chart review: If accessing medical charts without consent, a waiver of consent is required. Oral Consent: A waiver of signed consent is required. Subjects under 18 yrs old: Go to the next section. complete and attach assent information. Enter information in the Informed Consent table separately for each consent and/or waiver of consent.

Informed Consent Table

Title	Consent Type
Clean Consent - Vers. 04.09.18 - IRB18-008	Consent
IRB Stamped Approved Consent - Vers. 04.09.18 - IRB18-008	Consent

Informed Consent Table

Title (e.g. main, screening, translated, oral, information sheet, waiver request) *	Clean Consent - Vers. 04.09.18 - IRB18-008		
Consent Information Type*	Consent		
Consent Document*	X	Attachment	Clean Consent - Vers. 04.09.18 - IRB18-008

Who will obtain subjects consent? (Check all that apply)

- Principal Investigator
- Co-Investigator
- Study Coordinator
- Research assistant(s)
- Other research staff
- Contracted Data Collection Firm
- Other (please specify)

Informed Consent Table

Title (e.g. main, screening, translated, oral, information sheet, waiver request) *	IRB Stamped Approved Consent - Vers. 04.09.18 - IRB18-008		
Consent Information Type*	Consent		
Consent Document*	X	Attachment	IRB Stamped Approved Consent - Vers. 04.09.18 - IRB18-008

Who will obtain subjects consent? (Check all that apply)

X	Principal Investigator
X	Co-Investigator
	Study Coordinator
	Research assistant(s)
	Other research staff
	Contracted Data Collection Firm
	Other (please specify)

If consenting human subjects answer the questions below. If NOT consenting human subjects, leave blank and skip to the next section.

b) Describe the process used to consent all subjects on the study.

-Volunteer subjects will be identified in orthopedic office by Dr. Verdin or his staff
-Those interested in participating will be consented by Joseph M. Neal, MD at least 24 hours prior to their surgery. If possible, consent will be obtained in person. If not possible, consent will be obtained via phone.

c) Will subjects have as much time as they want between the explanation of the study and signing the consent form? If no, or N/A explain below. Y

d) If consent is being obtained from non-English speaking subjects, explain the translation process for all documents seen by subjects, including consent documents. Describe the consent process in these circumstances.

N/A

e) Do you plan on having a Legally Authorized Representative (LAR) involved in the consent process? If yes, explain below and ensure the appropriate section is included in the consent form. N

f) Will you require an impartial third party witness be included in the consenting process? If yes, explain below and ensure the appropriate section is included in the consent form. N

---

* * * Assent Background * * *

13. Assent Background (Continue to the next section if no subjects under the age of 18 will be enrolled in this study)

a) Complete the "Assent" table below. Attach assent documents and/or request assent waivers. Click "Help" above for more information regarding assent and assent waiver.

You must check children (under 18) on the Subject Checklist section to activate this table.

b) Complete the Regulatory Compliance worksheet below:

Regulatory Compliance - Subpart D - Children

Provide the specific age range for children (less than 18 years old) you wish to enroll in the study and what is

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your accrual goal:			
Age Range:		Total Accrual Goal:	
Check the appropriate box below (only one) to indicate which category your study may be approved in light of 45 CFR 46 subpart D for research involving children. Chlick on the links below for guidance.			
	Research not involving greater than minimal risk. 45 CFR 46.404		
	Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects. CFR 46.405		
	Research involving greater than minimal risk and no prospect of direct benefit to the individual child subjects involved in the research, but likely to yield generalizable knowledge about the subject's disorder or condition. 45 CFR 46.406		
	Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. 45 CFR 46.407		
	Will you be using an Assent Form? (Required for subjects 7-11 years old per BRI IRB policies - see 45 CFR 46.408 for reference)		
Describe in the space below the details of your assent process for children in your study. (Include specific approach(es) to subjects in various age ranges, how assent will be documented, who will be able to give persimssion for each child (e.g. child's parent(s) or guardian), and how this permission will be recorded in the file.)			
	Does your study involve an FDA regulated drug, device, or biologic? If yes, check the appropriate box below (only one) to indicate which category your study may be approved in light of 21 CFR 50 Subpart D for research involving children. Click on the links below for guidance.		
	Clinical investigations not involving greater than minimal risk 21 CFR 50.51		
	Clinical investigations involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects. 21 CFR 50.52		
	Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects.		
	Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. 21 CFR 50.53		
	Will you be using an Assent Form? (Required for subjects 7-11 years old per BRI IRB policies - see 45 CFR 46.408 for reference)		

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* * * HIPAA * * *

14. Health Insurance Portability and Accountability Act (HIPAA)

If you are using PHI and this page is not active you must return to the General Checklist and check the box regarding the use of PHI in this research.

HIPAA Privacy Rule: Establishes the right of an individual to authorize a covered entity, such as health plan, health care clearinghouse or health care provider, to use and disclose his/her Protected Health Information (PHI) for research purposes. The Privacy Rule defines the elements of individual information that comprise PHI and establishes the conditions under which PHI may be used or disclosed by covered entities for research purposes. It also includes provisions to allow an individual's PHI to be disclosed or used in research without the person's authorization (i.e., IRB Waiver of HIPAA Requirement Authorization). For more information refer to the HIPAA Privacy Rule.

Protected Health Information (PHI):Health information with one or more of the identifiers listed below. For more information see the NIH website. Research which involves the use of de-identified data is exempt from HIPAA requirements. In order to be de-identified data NONE of the subject identifiers listed below can be collected, used, reviewed, recoded, accessed or disclosed.

For more information see the following:VM/BRI Protected Health Information Guidance Document

a) How will you obtain approval to access PHI for this research?

X HIPAA Authorization request from subject

X Incorporated into consent form Stand alone document

Waiver of Subject HIPAA Authorization (partial or complete)(complete question e. below)

Limited Data Set and Data Use Agreement

Other: (explain below)

c) Will any non-VM/BRI personnel need access to PHI? If yes, how and where will they access subject PHI (e.g. on-site, remote via Cerner, etc.)? N

d) Review the following list and indicate if any of the information will be collected from any medical records for the purpose of this research project.

Names

Social Security Numbers

Telephone Numbers

All geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code, if according to the current publicly available data from the Bureau of the Census;

i. The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and

ii. The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.

All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.

Fax Numbers

Electronic Mail Addresses (email)

X Medical Record Numbers

i. You must identify the data points being collected from MRN by attaching a separate data collection sheet or listing them in the procedures section.

Health Plan Beneficiary Numbers

Account Numbers

Certificate/License Numbers

Vehicle Identifiers and Serial Numbers, including License Plate Numbers

Device Identifiers and Serial Numbers

Web Universal Resource Locations (URLs)

Internet Protocol (IP) Address Numbers

Biometric Identifiers, including Finger and Voice Prints

Full Face Photographic Images and any Comparable Images

Any other unique identifying number, character, or code (note this does not mean the unique code assigned by the Investigator(s) to code the research data)

e) Are you requesting a HIPAA waiver? (Required for any type of waiver of consent)If yes, answer the following questions. If no, proceed to the next section. N

i. Explain why the research cannot reasonably be conducted without the waiver of authorization:

ii. Explain why the research cannot reasonably be conducted without access to and use of identifiable health information:

iii. Describe the reasonable safeguards to protect idenifiable information from unauthorized use or re-disclosure:

iv. Describe the reasonable safeguards to protect against identification, directly or indirectly, any patient in any report of the research:

v. Describe the plan to destroy the identifiers at the earliest opportunity consistent with the research. If there is a health or research justification for retaining identifiers, or if law requires you to keep such identifying information, please provide this information as well:

vi. Provide written assurance that identifiable information will not be reused/disclosed to any other person or entity, unless such use is required by law, for oversight of the research study, or for other research permitted by law:

vii. Explain why the research is of sufficient importance to outweigh the privacy intrusion:

viii. Explain who the subject should contact to enforce patient rights, or to obtain an accounting of the research disclosures (e.g. PI, sub-investigator, coordinator):

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* * * Drugs and Devices * * *

15. Drugs and Devices

a) Does this study involve a drug or device? If YES, continue below.If NO, proceed to the next section. Y

i) Is the drug(s) or device(s) FDA approved? If YES, list drug / device name and explain in text field below. (e.g. HDE, 510K, Compassionate Use, etc) If NO, click "add" and complete the table below for each investigational drug(s) or device(s). Y

MRI

(These tables are not activated unless a drug / device question is checked on the General Checklist section)

b) Briefly describe the drugs and devices listed above. Include any relevant information that has not been

---

described in the protocol summary or background sections.

MRI will be used to obtain thigh scans

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* * * Potential Conflict of Interest * * *

16. Potential Conflict of Interest(This section is not enabled for exempt studies)/

a) Y Is there funding for this study?

b) N If yes, are there any positive financial disclosures related to this study for any key personnel?

c) N Regardless of funding, are there any positive positional disclosures related to this study for any key personnel?

d) Y I attest that I have read the 'https://brinet.benaroyaresearch.org/center/Documents/VM%20Research%20Conflicts%20of%20Interest.pdf#search=research%20conflict'target='blank'VM Conflict of Interest Policy and agree to abide by its terms. I will update this protocol when new or changes in conflict of interest arise, and I will comply with any conflict management plan required by the Institutional Review Board (IRB) to manage, reduce, or eliminate any actual or potential conflict of interest for the duration of the research.

If Yes to b) or c) above, complete the table and answer the questions below concerning the potential conflict of interest. If No, then proceed to the next section.

Minimizing Risks and Disclosure to Subjects

e) N Have you disclosed any actual, potential or perceived conflicts of interest in the consent form? Research Personnel are required to disclose all such conflicts to all research participants in the research consent form.

f) What steps, if any, have you taken or will you take to manage the conflict of interest and minimize the risks associated with any actual, potential or perceived conflicts of interest arising out of this research?

---

* * * Attachments * * *

16. Attachments

Attach relevant documents here. These could include:

- Collaborating Investigator's IRB approval and approved documents
- Conflict of Interest information
- Debriefing Script; Grant/Sub-contract
- HIPAA Authorization Form from HIPAA-covered entity
- Interview/Focus Group Questions
- Investigator's Brochure
- Letters of Agreement/Cooperation from organizations who will help with recruitment
- Questionnaires/Surveys
- Radiation Control Office approval material
- Recruitment Material (e.g., flyers, email text, verbal scripts)
- Protocol
- Patient Card
- Other files associated with the protocol (you can upload most standard file formats: xls, pdf, jpg, tif,

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etc.)

Please be sure to attach all documents associated with your protocol. Failure to attach the necessary files may result in this protocol being returned prior to review.

To update or revise any attachments, please delete the existing attachment and upload the revised document to replace it.

Select from list	Attachment Name	Attached Date	Submitted Date
Data Collection Sheet	IRB18-008 Copy of Study Data Sheet	03/08/2018	
Other	IRB18-008 Neal Financial Disclosure	03/08/2018	
Data Collection Sheet	IRB18-008 Copy of MRI Data Sheet	03/08/2018	
Protocol	Clean Protocol - Vers. 04.09.18 - IRB18-008	04/13/2018	04/13/2018

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* * * Obligations * * *

Note: The use of "I" below refers to the Principal Investigator (PI). If someone other than the PI is completing and submitting this application, that person is responsible to make sure the PI is aware of their obligation and assurances cited below. The PI is ultimately responsible for all conduct under this study and answers provided in this IRB submission.

Research Obligations of the Principal Investigator Include the Following:

Training - ALL key personnel, including any newly added personnel, must meet all IRB required training requirements (e.g. CITI Ethics, GCP, Conflict of Interest). Training refreshers must be completed at the appropriate intervals (i.e. every three (3) or four (4) years).

Study Modifications - Changes to any aspect of the study (e.g. protocol, consent/assent forms, advertising materials, additional key personnel, subject population, etc.) will be submitted to the IRB for approval before instituting the changes.

Final Report - The IRB will be notified when the study is complete, and must be closed out in eProtocol prior to expiration of the approval.

Investigator's Statement and Assurance of Confidentiality:

I certify that I have reviewed this application, including attachments, and all information contained herein is accurate to the best of my knowledge.

I agree to not enroll any subject(s) or collect any data intended only for research use prior to issuance of an IRB approval.

I understand that I am fully responsible for the execution and management of this study, and I am responsible for the performance of any sub-investigators or key personnel, including their adherence to all of the applicable policies and regulations.

I agree to report any substantive changes to the information contained in this application, unanticipated problems, or adverse events encountered during the project immediately to the IRB.

I will ensure the names of any human subjects or any identifiable data from human subjects shall be treated as confidential information. This information will not be disclosed to anyone other than those directly connected with the research project unless the patient has given prior approval in writing.

If this is a funded project, I certify that the funding source document is entirely consistent with the corresponding study protocol.

I certify I have not been barred from doing research by any regulatory agency or entity. If I am a physician (or other licensed health care professional), I certify that my medical (or other) license is current.

I further agree any failure to perform the undertaking specified above shall be good cause for termination of the research project.

When Closing Your Protocol:

I understand when I close this protocol with the IRB NO further data collection, follow-up with subjects, coding of data, data analysis, and manuscript preparation that requires personal identifiable information (e.g. PHI) may be conducted.

I agree to retain all research materials for at least 10 years after closure of the research project and acknowledge these documents may be subject to review by the Clinical Research Program and IRB, if deemed necessary.

I further certify I will not take any PHI and/or specimens generated from this research with me if I leave BRI/VM, unless having first established an agreement with VM legal in advance of my departure.

I confirm this study will not begin until the investigator receives written final approval or determination of exemption.

X The Principal Investigator has read and agrees to abide by the above obligations.

Continuing Review - You are responsible to complete and submit a Continuing Review form at least 30 days prior to the date of expiration. You will be asked to note accomplishments of your project at that time.

Protocol Deviations/Violations, Adverse Events (AEs) that occur in the course of the protocol will need to be submitted in a prompt manner from when they occurred.

X The Principal Investigator has read and agrees to abide by the above obligations.

Please click "next" to continue to protocol Check for Completeness. If the protocol is complete and ready for submission, please click "Submit Form" to your left to submit your protocol for IRB Review.

---

* * * Event History * * *

Event History

Date	Status	View Attachments	Letters
05/07/2020	CLOSED		
05/07/2020	FINAL FORM APPROVED	Y	N
04/27/2020	PROTOCOL EXPIRED		
04/24/2020	CONTINUING REVIEW 1 FORM Fox, Ellie added in CONTINUING REVIEW		
04/23/2020	FINAL FORM REVIEWER(S) ASSIGNED		
04/22/2020	FINAL FORM SUBMITTED	Y	
04/22/2020	FINAL FORM CREATED		
05/30/2019	CONTINUING REVIEW 1 FORM Stevens, Leslie added in CONTINUING REVIEW		
05/30/2019	CONTINUING REVIEW 1 FORM Chan, Christine added in CONTINUING REVIEW		
04/25/2019	CONTINUING REVIEW 1 FORM APPROVED	Y	Y
04/22/2019	CONTINUING REVIEW 1 FORM REVIEWER(S) ASSIGNED		
04/19/2019	CONTINUING REVIEW 1 FORM PANEL MANAGER REVIEW		
04/19/2019	CONTINUING REVIEW 1 FORM SUBMITTED	Y	

04/19/2019	CONTINUING REVIEW 1 FORM CREATED		
03/27/2019	REPORT 1 FORM WITHDRAWN		
03/27/2019	REPORT 1 FORM PANEL MANAGER REVIEW		
03/22/2019	REPORT 1 FORM SUBMITTED	Y	
03/13/2019	AMENDMENT 3 FORM APPROVED	Y	Y
03/01/2019	SAE REPORT 1 FORM APPROVED	Y	N
03/01/2019	AMENDMENT 3 FORM REVIEWER(S) ASSIGNED		
03/01/2019	SAE REPORT 1 FORM REVIEWER(S) ASSIGNED		
03/01/2019	AMENDMENT 3 FORM PANEL MANAGER REVIEW		
03/01/2019	REPORT 1 FORM CREATED		
03/01/2019	SAE REPORT 1 FORM SUBMITTED	Y	
03/01/2019	SAE REPORT 1 FORM CREATED		
02/06/2019	AMENDMENT 3 FORM SUBMITTED	Y	
02/06/2019	AMENDMENT 3 FORM CREATED		
05/31/2018	AMENDMENT 2 FORM APPROVED	Y	Y
05/30/2018	AMENDMENT 2 FORM REVIEWER(S) ASSIGNED		
05/29/2018	AMENDMENT 2 FORM SUBMITTED	Y	
05/29/2018	AMENDMENT 2 FORM CREATED		
05/24/2018	AMENDMENT 1 FORM APPROVED	Y	Y
05/23/2018	AMENDMENT 1 FORM REVIEWER(S) ASSIGNED		
05/22/2018	AMENDMENT 1 FORM SUBMITTED	Y	
05/17/2018	AMENDMENT 1 FORM CREATED		
04/30/2018	NEW FORM APPROVED	Y	Y

04/30/2018	NEW FORM UNDO APPROVED		
04/30/2018	NEW FORM APPROVED	Y	Y
04/17/2018	NEW FORM REVIEWER(S) ASSIGNED		
04/13/2018	NEW FORM REVIEWER(S) ASSIGNED		
04/12/2018	NEW FORM PANEL MANAGER REVIEW		
03/08/2018	NEW FORM PANEL ASSIGNED		
03/08/2018	NEW FORM SUBMITTED	Y	
[redacted]	[redacted]		

BENAROYA RESEARCH INSTITUTE
Virginia Mason

NOTICE OF IRB EXEMPTION

[redacted]

Joseph Neal, MD
Anesthesiology

RE: IRB# IRB18-008 (NEW)
Study Title: Defining Normal Postoperative Magnetic Resonance Imaging after Total Knee Arthroplasty

Dear Joseph Neal, MD,

Thank you for submitting the above referenced study for review by the Benaroya Research Institute at Virginia Mason Institutional Review Board (BRI IRB). Review was carried out in light of federal regulations on human subjects and BRI IRB policies.

[redacted]

During the course of the study, if there are changes in the protocol that would alter this determination (e.g. increased risk, additional non-exempt activity), including protocol termination, or if human subjects involved in the study are subjected to unanticipated problems, please report these immediately to BRI IRB. Please include the Protocol ID Number (IRB18-008) on all correspondence.

If your study received initial Feasibility Review, no study activity may occur until you receive a Clinical Research Program letter to commence from the BRI Administrative Director of Clinical Research, Cheryl Weaver. Her phone number is (206) 342-6911.

Please contact the Research Protections Department at irb@benaroyaresearch.org if you have any question regarding your approval or the eProtocol system. Thank you.

Sincerely,

Bredfeldt, James, MD
IRB Chair

Items included with this submission are listed below under attachments:

Attachments

Clean Protocol - Vers. 04.09.18 - IRB18-008

Notes:
Additional approved documents: IRB Stamped Approved Consent - Vers. 04.09.18 - IRB18-008

Benaroya Research Institute at Virginia Mason

1201 Ninth Avenue, Seattle, WA 98101
p 206.342.6500 f 206.342.6580
BenaroyaResearch.org

BENAROYA
RESEARCH INSTITUTE
Virginia Mason

FINAL AUTHORIZATION TO COMMENCE CLINICAL RESEARCH

DATE: August 16, 2018

TO: Joseph Neal MD, Principal Investigator
Leslie Stevens , Dept. Manager
Maria Prado, Study Coordinator

FROM: Cheryl Weaver, Administrative Director
Sylvia Cooper, CRP Specialist

RE: CRP18023 / IRB18-008

TITLE: Defining Normal Postoperative Magnetic Resonance Imaging after Total Knee Arthroplasty

	Days
Feasibility Submission to Approval	33
IRB Submission to Commencement Notification	125
Total	158

This correspondence is to inform you that BRI's Clinical Research Program Administration has the following required documentation in our file for the above mentioned clinical research study:

1. BRI Feasibility email approving submission of your study to the IRB
2. IRB approval for the conduct of this study

Please remember, by proceeding with this project you are agreeing to comply with all regulations, (Institutional, State, Local and Federal) for Principal Investigators, as well as, those that guide the ethical conduct of clinical research. Any proposed changes or amendments to the project must be authorized by the Institutional Review Board, before they may be implemented.

We expect that your trial will accrue in a timely fashion and look forward to reviewing enrollment activity within 60 days of this authorization.

Sincerely,

Cheryl Weaver, CCRC, CCRA
Administrative Director, CRP
cweaver@benaroyaresearch.org

CC: Research Protections Department
Tina Lencioni, Contract Administrator
Johnson Kukundakwe, Clinical Research Accountant
CRP Quality Assurance Department
Gail Chumbley, CRP Financial Manager
Erica Lacaden, Billing Specialist
David Caldwell, Communications Specialist

Protocol Title: Defining Normal Postoperative Magnetic Resonance Imaging after Total Knee Arthroplasty

Date Submitted: Draft

Approval Period: Draft

Important Note: This Print View may not reflect all comments and contingencies for approval. Please check the comments section of the online protocol. Questions that appear to not have been answered may not have been required for this submission. Please see the system application for more details.

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* * * [redacted] * * *

ADVERSE EVENT REPORT FORM

1. Is this adverse event unexpected (in terms of nature, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, or the Investigator Brochure; and (b) the characteristics of the subject population being studied? Y
2. Is this adverse event related or possibly related to participation in the research (possibly related means there is a reasonable possibility the incident, experience, or outcome may have been caused by the drugs, devices or procedures involved in the research)? Y
3. Does this adverse event suggest the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized? Y

(Note: "off-site" reports will not be accepted unless; (a) the event described is both serious and unexpected,(b) the report identifies all previous safety reports concerning similar adverse experiences,(c) the report analyzes the significance of the current adverse experience in light of the previous reports, and (d) the report outlines a corrective action plan. 21_CFR_312.32)

If you answered "NO" to any of the above questions STOP. You do not need to submit this event/report to the IRB unless all three above criteria are met.

4. What type of report is this?

X Initial Report

Date of Initial Report: 03/01/2019

Follow up #

Follow up complete

Drug

Device

N/A [Name of test article(s)]:

5. Describe in [redacted] you are reporting (e.g. Confusion, Vomiting, Hyponatremia, etc.):

Catheters used for continuous adductor canal block contain wire. According to the manufacturer's published information, these catheters are deemed "MRI Conditional", with low to no risk from heating during an MRI scan.
Our first subject had their MRI on February 22, 2019 and reported a mild sensation of heating at the catheter site. The MRI was aborted. The patient reported no harm.
Dr. Neal became aware of this issue on February 25, 2019. After consultation with Drs. Blackmore, Strodtbeck, Warren, and Macdonald, it was agreed that the adductor canal catheter will be removed in subsequent patient volunteers that are recruited for this study.

6. Event Start date: 02/22/2019

7. Date of Death (if applicable):

8. Participant Study Identifier: Number 6

9. Why do you consider this event unexpected?

The manufacturer does not report significant heating to be an issue with these catheters. Furthermore, these catheters have indeed been in place in some patients who underwent uneventful MRI studies at Virginia Mason.

---

10. Relationship to research:

Definite

Probable

Possible (possibly related means there is a reasonable probability that the incident, experience, or outcome may have been caused by the drugs, devices or procedures involved in the research.)

11. Why do you consider this event related or possibly related to participation in the research?

Warming at the catheter site is consistent with MRI effects on metallic objects

12. What changes do you propose to the consent form and/or the protocol in order to protect the rights, welfare and safety of the research subjects? If none are proposed, provide the rationale for why changes are not needed?

13. Where did the unanticipated Adverse Event occur? (i.e. on site or off site) If "ON SITE" (e.g. occurred to VM/BRI subject) where did the AE occur? (e.g. VM, BRI, at home etc.):

VMMC 5th floor MRI scanner

14) Choose an adverse event category:

Death		Life-Threatening	Disability	Hospitalization
Congenital Anomaly	X	Required intervention to prevent damage / impairment	Medically Important Event	Other: (explain below)

Because the patient reported heating, the MRI was terminated. The heating immediately dissipated and the patient reported no further harm.

15) Date the PI/study staff became aware of this event: 2/25/19

16) Description of event:

As noted above

17) Has this event been reported to all appropriate agencies as defined in the protocol, grant, contract, or clinical trial agreement? Check all that apply and provide date reported:

Sponsor: N/A

Date Notified:

FDA (if BRI/VM PI holds the IND/IDE): N/A

Date Notified:

Coordinating Center: N/A

Date Notified:

18) Has this type of event been reported previously to the BRI IRB? If yes, explain. N

I am unaware of any previous reports

19) Do you consider the frequency higher than expected? If yes, explain. Y

The event was unexpected based on previous experience and manufacturer report. What is unclear is the precise intensity of the heating reported by the patient. It is possible that other patients have experienced similar sensations, but have not reported them.

20) Is this study closed to new accrual at VM (and its affiliated sites)? N

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i. If yes, is at least one (1) participant at VM (and/or its affiliated sites) still receiving study treatment/intervention?

21) if "yes" you will need to also complete an amendment form and attach the revised protocol and/or consent form with all changes underlined?

Protocol Title: Defining Normal Postoperative Magnetic Resonance Imaging after Total Knee Arthroplasty

Date Submitted: 05/29/2018

Approval Period: Draft

Important Note: This Print View may not reflect all comments and contingencies for approval. Please check the comments section of the online protocol. Questions that appear to not have been answered may not have been required for this submission. Please see the system application for more details.

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Protocol Amendment 1) Complete the questions below.2) Update your approved protocol including any attachments.3) Electronically "sign" your application by clicking the check box in the Obligations section.4) Remember to click "Submit Form" so the IRB staff will receive your request.5) For Cooperative studies (see help above). Answer all questions below from BRI/VM specific perspective.

1. Does this amendment change the status of your study?If yes, check one of the boxes below and complete the table. If no, continue to question 2. N

Study Status Change

	Temporary Closure to Accrual	Date Effective:	
	Reason:		
	Permanent Closure to Accrual, Study Particpation/Intervention Continues	Date Effective:	
	How many subjects were ever enrolled at this site?		
	How many subjects are still on treatment at this site?		
	How many subjects (total of all sites) were enrolled in this study (if applicable and know)?		
	Permanent Closure to Accural, Only Long-Term Follow-Up and/or Data Collection/Analysis Continues (no active participation/intervention continues)	Date Effective:	
	How many subjects were ever enrolled at this site?		
	How many subjects (total of all sites) were enrolled in this study (if applicable and know)?		

2. Describe all changes being proposed including any modifications to the attached documents. (If referencing attachments cite page numbers)

1. Inclusion of stipend for participants
2.

3. Will the requested modifications change the scope or research objectives (e.g. change in specific aims, change from previously approved use of human subjects, etc.)? If yes, describe below. N

4. Are any NEW potentially vulnerable subjects being added as targeted or possibly included in this study (e.g. children, pregnant women, illiterate, etc.) ? N

If yes, define your new study population and provide steps to protect the population. (Update the assent section if children are being added.)

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5. Were changes made to the Consent Form? (If no consent, or no changes check "No" and proceed to question 6) Y

If yes, describe changes below and provide justification regarding your plan to re-consent subjects. Then, check the appropriate box(es) below. Once this modification is approved, the IRB will hold the researcher responsible to "re-consent" all subjects as indicated.

Inclusion of stipend and modification of MRI timing

Re-consent not required
X Consent all new subjects with modified consent form(s)
Re-consent active participants at next visit
Re-consent all subjects including those who have completed the study
Other: (explain)

6. Indicate level of risk involved with the changes proposed.
(If level of risk has changed, update the "Risk" section in the protocol.)

Increase X No Change Decreased

7. If this study was originally reviewed Expedited, do you attest this project continues to present no more than minimal risk of harm to subjects? See the Help section for more information. Y
If no, your study may be reviewed by the Full Board IRB.

Approval Includes

List of sections (and questions) that have been changed/modified

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* * * Personnel Information * * *

Click "Help" (upper right corner of screen) for guidance regarding who to include below (Key Personnel) and what CITI Training is needed. See the Clinical Research Glossary for definitions. Questions: Contact the Research Protections Department

Principal Investigator

Client defines "Investigator" as an individual who conducts a research study. If the study is conducted by a team of individuals, the Investigator is the responsible leader of the team.				
Name of Principal Investigator*		**Degree (MD/PhD/BSN/etc.)**		**Title**
Neal, Joseph		MD		ANESTHESIOLOGIST
Email*		**Phone**		**Fax**
Joseph.Neal@virginiamason.org		206-223-6980		
VM/BRI Department		**Investigator Affiliation Check ALL that apply***		**Mailstop**
Anesthesiology	X	VM personnel		B2-AN
		BRI personnel		**Zip code**
		Other		98101
Training Details				

No training data is available.

Sub-Investigator(s)

Sub-Investigator	Degree (MD/PhD/BSN/etc.)	Title	Research Department
Blackmore, Craig	MD	RADIOLOGIST	Radiology MD Admin
Verdin, Peter	MD	ORTHOPEDIC SURGEON	Orthopedics - Outpatient
Jackson, Dane	MD	RESIDENT - RADIOLOGY	Graduate Medical Education

Sub-Investigator(s)

Name of Sub-Investigator(s)
Blackmore, Craig

Degree (MD/PhD/BSN/etc.)
MD

Title
RADIOLOGIST

Email*
Craig.Blackmore@virginiamason.org

Phone
206-223-6851

Fax

VM/BRI Department
Radiology MD Admin

Investigator Affiliation Check ALL that apply*
X VM personnel
BRI personnel
Other

Mailstop
R3-324

Zip code
98101

Role in Study
Radiologist

Training Details

No training data is available.

Sub-Investigator(s)

Name of Sub-Investigator(s)
Verdin, Peter

Degree (MD/PhD/BSN/etc.)
MD

Title
ORTHOPEDIC SURGEON

Email*
Peter.Verdin@virginiamason.org

Phone
206-223-7530

Fax
X6-ORT

VM/BRI Department
Orthopedics - Outpatient

Investigator Affiliation Check ALL that apply*
X VM personnel
BRI personnel
Other

Mailstop

Zip code
98101

Role in Study

Training Details

Course	UserID	CourseCompletionDate	CourseExpirationDate
CITI Good Clinical Practice	peter.verdin	11/14/2016 3:34:28 PM	11/14/2019 3:34:28 PM
Human Research	peter.verdin	11/8/2015 4:18:51 PM	11/7/2018 9:00:00 PM

Sub-Investigator(s)

Name of Sub-Investigator(s)
Jackson, Dane

Degree (MD/PhD/BSN/etc.)
MD

Title
RESIDENT - RADIOLOGY

Email*	Phone	Fax
Dane.Jackson@virginiamason.org	206-583-6079	
VM/BRI Department	**Investigator Affiliation Check ALL that apply***	**Mailstop**
Graduate Medical Education	X VM personnel	
	BRI personnel	**Zip code**
	Other	
Role in Study	Masked assessment of MRI results	

Training Details			
Course	**UserID**	**CourseCompletionDate**	**CourseExpirationDate**
CITI Good Clinical Practice	dane.jackson	10/21/2017 3:19:35 PM	10/20/2020 3:19:35 PM
Human Research	dane.jackson	10/20/2017 2:09:36 PM	10/19/2020 2:09:36 PM

Study Coordinator

Study Coordinator	Degree (MD/PhD/BSN/etc.)	Title	Research Department
Neal, Joseph	MD	ANESTHESIOLOGIST	Anesthesiology

Study Coordinator

Name of Study Coordinator	Degree (MD/PhD/BSN/etc.)	Title
Neal, Joseph	MD	ANESTHESIOLOGIST
Email*	**Phone**	**Fax**
Joseph.Neal@virginiamason.org	206-223-8822	
VM/BRI Department	**Investigator AffiliationCheck ALL that apply***	**Mailstop**
Anesthesiology	X VM personnel	B2-AN
	BRI personnel	**Zip code**
	Other	98101

Training Details
No training data is available.

Regulatory Contact (Primary IRB contact if not PI or Study Coordinator)

Name of Regulatory Contact		Degree (MD/PhD/BSN/etc.)	Title
Email*		**Phone**	**Fax**
VM/BRI Department		**Investigator Affiliation Check ALL that apply***	**Mailstop**
		VM personnel	
		BRI personnel	**Zip code**

		Other		

Training Details

No training data is available.

Additional Personnel Information: (Use the area below if necessary to provide additional information regarding the personnel on this protocol)

Dr. Lauren Steffel, Puget Sound VA Health Services, will participate in manuscript writing and data analysis. She will have no contact with Virginia Mason subjects. The data that she will have access to will be de-identified with regard to subject PHI.

* * * Subject Checklist * * *

Subject Checklist

Select all that apply:

Retrospective medical records (e.g. Chart Review)

Tissue, blood, other specimens (e.g. repository)

X Individuals with underlying medical conditions

X Healthy individuals

Select all vulnerable groups:

Check all targeted or possibly included subjects. This also applies to retrospective chart reviews.

Some groups (e.g. prisoners, pregnant women, or children) may require additional IRB oversight per federal regulations.

Prisoners

45CFR46 Subpart C (Should be excluded unless you know subject(s) will be "in prison" at the time of enrollment. Notify IRB immediately if a subject becomes incarcerated after enrollment. This population can not be reviewed exempt.)

Pregnant women

45CFR46 Subpart B

Females of childbearing potential

Children (under 18)

45CFR46 Subpart D

Persons incompetent to give consent (e.g., dementia, comatose, have legally authorized representative)

Economically/educationally disadvantaged.

Illiterate

Non-English speaking

See: VM Interpreter Services

Are any other subjects outside of the above targeted or possibly included in this study? N

If yes, describe below:

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* * * Study Location * * *

Study Location

1. Click "add" and create a separate row in the table below for each unique VM / BRI study location.

VM/BRI Table

VM Location	Other VM Location:	VM location Study Activities	Other Activities
Main Campus Seattle - Clinic / Hospital		Blood draw, Informed consent discussion, Ongoing study visits, Screening visits, Specific procedures associated with the study	

VM/BRI Table

Location Main Campus Seattle - Clinic / Hospital

Activity Blood draw,Informed consent discussion,Ongoing study visits,Screening visits,Specific procedures associated with the study

2) Are there any locations outside of VM / BRI that are involved in any way with this study? If yes, explain below. If no, proceed to the next section. N

i. Are any outside locations "engaged"with this research study? If yes, explain: (click on "Help" for more information regarding engagement) N

ii. Will the BRI IRB be responsible for oversight (IRB of Record) for any study procedures conducted at outside locations? If yes, describe in the table below (click "add"). If no, confirm who is the IRB of Record for engaged activities outside of VM in the space below and then proceed to the next section. N

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* * * General Checklist * * *

General Checklist

Select All That Apply: At least 1 box must be checked to proceed. If none are applicable contact the IRB at IRB@benaroyaresearch.org Use the attachment section to add separate documents or forms.

X Protected Health Information (PHI) will be viewed, created, accessed, used, or disclosed by VM/BRI personnel or others. (Checking this box activates the HIPAA section)

Questionnaire/Survey

Tissues or data to be stored for future research projects (e.g. registry or repository)

Tissues or data to be sent out of VM / BRI as part of a research agreement - Material Transfer Agreement

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(MTA)- Data Use Agreement (DUA)

X FDA regulated device (Investigational or otherwise)- This includes Humanitarian Use Devices (HUD)

FDA regulated drugs, reagents, or chemicals (Investigational or otherwise)

This study is or will be posted on ClinicalTrials.gov

If checked, specify number:

Radioisotopes/radiation-producing machines, even if standard of care (Radiation Safety)

VM/BRI Institutional Biosafety Committee (IBC) Review Required- Clinical research involving recombinant and/or synthetic nucleic acid

Request to Rely on Another IRB - Please upload completed Request to Rely and associated documents in attachment section (This applies for Cooperative Review studies.)

IRB Authorization Agreement (IAA), Memorandum Of Understanding (MOU), etc.(attach in the Attachments section (This only applies to studies where the Client IRB is the "Reviewing" IRB).

X A stand-alone protocol already exists.

Checking this box doesn't reduce the number of questions you need to answer. However, you can be brief with your answers and include references to the stand-alone protocol (e.g. section, page #) for more information. Use the attachment section to include the stand-alone protocol with your submission.

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* * * Funding * * *

Funding / Resources

1) Is there funding or other resources required for this project? Y

No means absolutely no internal or external funds, services, skills, or products (e.g., statistical services, database warehousing, free test article) are provided. If no, proceed to the next section.

If yes, Click "add" and create a separate row in the table below for each unique funding source.

Funding / Resources Table

Funding Name	BRI Funding #	Restricted BRI Funds	Unrestricted BRI Funds	Federal Grant	Federal Funding #, Grant #	Non-Profit Foundation	Industry Funding
Washington State Society of Anesthesiologists Seafair Grant Award	Through VM Foundation	N	N	N		Y	N

Funding / Resources Table

Name of Funding Entity: Washington State Society of Anesthesiologists Seafair Grant Award

BRI Funding Number: Through VM Foundation

BRI restricted funds? N

BRI unrestricted funds?	N
Federal Grant funds?	N
Non-Profit Foundation?	Y
Industry Funding	N

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* * * Application Type Checklist * * *

Please check one of the boxes below to determine how to move forward with your project. The US Office of Human Research Protections (OHRP) has created graphic aids to help with deciding if your research requires IRB oversight. In addition, please contact the BRI Research Protections Department with questions.

Application type checklist

Not Human Subjects Research (This form is not currently available through eProtocol. Please click "https://www.benaroyaresearch.org/sites/default/files/Human%20Subjects%20Determination%20Form.doc" target=_blankhere if applicable.)

Exempt

X Expedited/Full Board (This includes Cooperative and Chart Reviews.)

Indicate what level of review you anticipate for this protocol:

Full Board (greater than minimal risk)

X Expedited (minimal risk)

"https://www.benaroyaresearch.org/our-research/clinical-research/for-investigators/starting-study/cooperative-trials" target=_blankCooperative (approval by another IRB of record, regardless of risk level)

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* * * Expedited Paragraphs * * *

EXPEDITED REVIEW CATEGORIES If this is a FULL BOARD study, or COOPERATIVE (IRB of Record is not BRI), then proceed to next section.

For expedited review all aspects of the research must be: (1) Minimal Risk (2) Involve one or more categories listed below. Select all that apply (Click Help for more information):

1. Clinical studies of drugs and medical devices only when condition (a) and (b) are met.

   a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

   b) Research on medical devices for which

      i) An investigational device exemption application (21 CFR Part 812) is not required; or

      ii) The medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

X 2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

   a) From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

   b) From other adults and children, considering the age, weight, and health of the subjects, the

collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by non-invasive means.

Examples:

a) Hair and nail clippings in a non-disfiguring manner.

b) Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction.

c) Permanent teeth if routine patient care indicates a need for extraction.

d) Excreta and external secretions (including sweat).

e) Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue.

f) Placenta removed at delivery.

g) Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor.

h) Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.

i) Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings.

j) Sputum collected after saline mist nebulization.

X 4. Collection of data through non-invasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples:

a) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy.

b) Weighing or testing sensory acuity.

c) Magnetic resonance imaging.

d) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography.

e) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

X 5. Research involving materials (data, documents, records, or specimen) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (NOTE: Some research in this paragraph may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

6. Collection of data from voice, video, digital, or image recordings made for research purposes.

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category

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may be exempt from the HHS regulations for the protection of human subjects - 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

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* * * Summary, Purpose, Procedures * * *

BRI Study ID Number - From the Clinical Research Program (e.g. CRP170XX)

CRP18023

Unit / Department - Administrative Oversight of Research

Defining Normal Postoperative Magnetic Resonance Imaging after Total Knee Arthroplasty

1. Summary

Provide a summary of the scope of work of this protocol.

Recent reports(1) describe sentinel cases of presumed local anesthetic-induced myotoxicity occurring after continuous adductor canal blocks (CACB) that were placed to provide analgesia after total knee arthroplasty (TKA). Crucial to the diagnosis, management, and eventual understanding of this newly described anesthetic complication is elucidating what constitutes normal postoperative magnetic resonance imaging (MRI) after TKA. A recent retrospective review of MRIs obtained for various indications within a week of TKA failed to identify a consistent pattern of MR findings that might have defined "normal MRI imaging" after TKA (BRI 16092, Magnetic Resonance Imaging of the Quadriceps Muscle After Total Knee Arthroplasty). The logical next step in this investigation would be to obtain MRIs in TKR patients just prior to hospital discharge after an otherwise normal postoperative course.

2. Purpose

Describe the purpose for the proposed project as well as the hypotheses/research questions to be examined.

This study aims to define normal quadriceps imaging in 20 asymptomatic volunteers one to two days after undergoing TKA. A secondary aim is to investigate alterations in creatine phosphokinase (CPK) and aldolase levels coincident with TKA. The aim of this observational study is to define what constitutes a normal MRI appearance and normal CPK / aldolase alterations in postoperative TKA patients. This knowledge is crucial for proper diagnosis and further understanding of this sentinel complication.

3. Procedures

a) Describe the activities/procedures to be conducted in chronological order (e.g. pull charts/data from Cerner, screening, interventions/interactions with subjects, data collection, photographing, audio and video recording, follow-up.)

-Patients of various age and sex that are scheduled for unilateral TKR will be approached by VM orthopedic surgeons to ascertain their willingness to volunteer for this study
-Identified patients will be consented for study participation by the PI at least 24 hours prior to their entry into the study
-All patients will undergo the standard VMMC TKA clinical pathway, which includes a 1 to 2 day continuous adductor canal block
-If their postoperative course has been normal, These patients will have pre- and post-op CPK and aldolase levels analyzed.
-Leg MRIs will be graded using a standardized checklist by a supervised radiology resident who is unaware of the study's purpose.

b) Explain who will conduct the procedures. Include where and when they will take place.

-MRIs will be obtained as scheduled cases at VMMC
-CPK and aldolase will be obtained and analyzed by VMMC laboratory
-MRIs will be assessed using a standardize template by a radiologist who is unaware of the study's purpose

c) Will you be conducting procedures directly with patients? If yes, answer the questions below. If no (e.g. chart review only), proceed to question 4.0 Study Duration. Y

i) Are there any procedures considered experimental and outside standard of care or established practices at Virginia Mason, including follow-up procedures? Y

If yes, explain.

Lower extremity MRIs are standard, but are not a routine part of postoperative TKA care. CPK and aldolase analyses before

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and after TKA is non-standard.

ii) Will blinding be involved with this study? Y

If yes, explain.

-The interpreting radiologist will be blinded as to the study's purpose

iii) Will deception be used? N

If yes, provide a rationale and describe debriefing procedures. Submit a debriefing script in attachments section.

iv) Will audio, photographs, or video taping of individuals occur? N

If yes, describe and clarify what will become of the tapes/photographs (e.g., shown at scientific meetings, erased, etc.).

4. Study Duration

What is the anticipated start date and duration of the proposed study?

We plan to start immediately after IRB approval. We anticipate all 20 volunteers should be recruited and studied within a 3 month period

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* * * Background and additional procedures * * *

5. Background and additional procedures

a. Relevant Background: Discuss the present knowledge, appropriate literature and rationale for conducting the research.

Local anesthetics consistently induce myotoxicity in animal models and in up to 0.5% of humans after ophthalmic blocks, yet clinically apparent myotoxicity in patients undergoing peripheral nerve blocks was heretofore believed to be nearly non-existent.(2) This changed after introduction of continuous adductor canal blocks (ACB) at Virginia Mason Medical Center when 4 patients developed symptoms, MRI findings, and neurophysiologic testing compatible with local anesthetic-induced myotoxicity. In short order, other cases were reported from the Swedish Orthopedic Institute, 3 from retrospective analysis of other post-TKA MRIs obtained at Virginia Mason, and anecdotally from practices throughout the United States. These sentinel complications have resulted in major morbidity for the affected patients. After a normal early postoperative course, the patients rapidly developed flaccid quadriceps muscles and the inability to lift the operative lower extremity against gravity, with consequent halting of their rehabilitative trajectory. While fortunate patients recovered fully or nearly so after weeks to a few months as the unaffected myoblasts regenerated, less fortunate patients have never recovered to baseline.

Because non-ophthalmic myotoxicity has never been described to this degree in humans, little is known about its etiology, diagnosis, and treatment. Definitive diagnosis of myositis requires muscle biopsy, but this invasive and expensive intervention is unlikely to occur. All patients in our series had MRI signals consistent with edema and inflammation, consistent with myositis. However, the radiologic literature is silent with regard to what constitutes normal MRI findings immediately after TKA. Therefore, the MRI pathology that we observed, while clearly demonstrating inflammatory changes in the anterior compartment of the leg, could conceivably represent normal postoperative findings. We have attempted to study this question by retrospectively reviewing MRIs of patients who underwent leg MRI within a week of TKA. While we could identify several patients with clinical presentations consistent with undiagnosed myotoxicity, we were unable to confidently discern pathological findings versus 'normal' postoperative changes on imaging.

b. If applicable, please describe statistical methods of the research and plans for analysis of the data (i.e. planned statistics, justification of sample size, etc.).

Observational convenience sample, therefore N/A

c. Are there any alternative treatments to participating in this research (e.g., standard of care treatment, etc.)? N

If yes, describe. Any standard treatment that is being withheld must be disclosed. This information must be included in the consent form.

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d. Can subjects receive alternative treatment outside of enrolling in this study? N/A

e. Will subjects be followed after their participation is complete? N

If yes, explain why and describe how:

f. Is this a cooperative study (e.g. UW, FHCRC is IRB of record)? N

(If yes, answer the questions below. If no, proceed to the next section. Click here for more information.)

i. Has this study been approved by the IRB of record? (NOTE: BRI IRB cannot review any COOP study not currently approved by the IRB of record)

If yes, when did the initial approval for this study occur?

ii. Has this study undergone Continuing Review (CR) at the IRB of record?

If yes, what are the current approval dates?

iii. Will there be any costs to VM for study procedures (e.g. lab costs, etc.)?

If yes, how will these costs be paid to VM? (e.g., direct billing to your grant, etc.)

iv. Will potential subjects from VM be approached?

(Note: Refer to Non-VM Investigator Patient Approach Procedures for the correct procedures.)

If yes, describe how subjects will be approached and by whom.

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* * * Subject Population * * *

6. Subject Population

a) Complete the projected subject enrollment information below:List multiple subject groups/cohorts as appropriate.(e.g. retrospective, prospective, children, adult, controls, treatment, etc.)

Subject Enrollment

Subject Group (DEFINE: cases/controls/records/ specimens etc.)	Age Range	Expected Number at End of Study (locally)	Expected Number at End of Study (Total if multi-site)	Expected Enrollment next 12 months
20	50-75	20		20

b) Complete the vulnerable subject table below:

Potentially Vulnerable Subject Populations

	Targeted	Possible Inclusion	Excluded	N/A
Prisoners: FAQ (Note: should be excluded unless you know subjects will be "in prison" at the time of enrollment. Notify IRB immediately if a subject becomes incarcerated after enrollment.)			X	
Pregnant Women: (45CFR Subpart B)			X	
Children (under 18): 45CFR46 Subpart D			X	
People not competent to provide informed consent			X	
If the above populations are targeted or possibly included, explain: (Give rationale and specific steps to protect those populations)				
Female of childbearing potential:			X	
If excluded, explain:				
Non-English Speaking: VM Interpreter Services			X	
If Non-English Speaking subjects are targeted or possibly included, give rationale and specific steps to protect those populations. If excluded, explain.	Concern regarding not fully understanding through the translator that this study involves the acquisition of MRI and enzyme tests that are not part of a standard knee replacement hospitalization			
New Description	New Description	New Description	New Description	New Description
New Description	New Description	New Description	New Description	

c) Are any other potentially vulnerable subjects (sight impaired, illiterate, etc.) targeted or possibly included in this study? If yes, explain and provide steps to protect this population: N

d) Inclusion and Exclusion Criteria (e.g., Participants must have 20/20 vision, Participants must be 30-45 years of age, etc.)

i. Identify inclusion criteria.

-Anticipated unilateral TKA performed under the standard VMMC joint pathway, with 1 to 2 night stay postop
-Subjects will be operated by a single surgeon (Dr. Verdin) to eliminate possible confounders related to surgical technique
-Subjects must be willing to volunteer for MRI study and CPK and aldolase blood draws

ii. Identify exclusion criteria.

-Any contraindication to use of spinal anesthesia or adductor canal-based analgesia
-History of muscle wasting or related disease
-History of auto-immune disorders that may affect the musculature
-History of pre-existing neurologic condition affecting the lower extremities
-Allergy to radiologic contrast
-Contraindications to MRI exam

e) To provide support for your projected enrollment goals, how many patients at VMMC do you anticipate would have met your eligibility criteria over the last 1-5 years? If NA or no numbers available, explain why and provide rationale to support your projections:

1000 per year

f) How long do you anticipate it will take to complete accrual for this study?

3 months

* * * Recruitment Process, Subject Compensation and Costs * * *

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7. Recruitment Process:

a) Describe the step-by-step procedures for identifying and recruiting potential research subjects and/or requesting their data or specimens.

-Patients of various age and sex that are scheduled for unilateral TKA will be approached by Dr. Verdin to ascertain their willingness to volunteer for this study
-Identified patients will be consented for study participation by the PI (Dr. Neal) at least 24 hours prior to their surgery

b) Identify who will contact prospective subjects. (complete request for waiver of consent if applicable)

Joseph M. Neal, MD

c) Planned Subject Identification Methods:

VM Medical Records / Chart Review	Direct Advertising
From PI's own practice / department Records	Referrals
Specific registries, specify IRB#:	
Outside Institution, please specify:	

X Other, explain below:

From VMMC orthopedic surgical patients scheduled for TKA. Initial willingness to participate in the study will be ascertained by Dr. Verdin or his physician assistant.

d) Planned Recruitment Materials / Methods:

X Face to face interactions	Flyers / posters
Phone Scripts	Letters to providers / schools / organizations
Television ads	Newspaper ads
Letters to prospective subjects	Radio ads
Oral Scripts	PowerPoint presentations
Internet ads / postings	Email
X Other, please specify:	Phone conversation with PI

NA

Attach ALL recruitment information in its final form using the Attachments section of this IRB eProtocol form.

See BRI IRB Recruitment Material Guidance.

8. Subject Compensation and Costs:

a) Will subjects or their health care providers be required to pay for any study related procedures or products? N

i. If "Yes," explain. Max out of pocket? Are any funds available from the study if the subjects insurance will not cover study-related procedures or products?

b) Will subjects receive compensation in any manner for participation? If "Yes," complete the questions below. If "No", skip to the next section. Y

i. Will subjects receive monetary payment? If yes, describe payment schedule including per visit and total. Y

$50 stipend will be paid after the participant has completed the study (paid as gift card)

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ii. Will any one payment be more than 40% of total compensation? If "Yes," explain and provide rationale. N

iii. Will other forms of compensation be provided? If yes, describe below. Y

	Parking Voucher	Gifts
	Transportation	Lodging
X	Gift card/certificate	Other (describe below)

As noted above

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* * * Risks * * *

9. Risks / Data Safety Oversight / Monitoring

(Click "Help" above for more information)

a) PI's evaluation of the overall level of Risk. (Please check one: minimal, or greater than minimal.) Minimal risk: The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life, or during the performance of routine physical or psychological examinations or tests.

X Minimal risk

Greater than minimal risk

b) Check all potential risks/side effects to subjects. Check only added potential risks/side effects that may occur to subjects from the research and not those that would occur if subjects were to receive standard treatment/procedures only. [Note: Virtually all research studies involve "breach of confidentiality" and "invasion of privacy" as potential risks since several entities may have access to research records (e.g., FDA, NIH, IRB, etc.). Risks must be consistent with the consent form and protocol.]

Risk / Side Effects

Physical Harms		Psychological		Social Economical	
	Minor Pain		Depression	X	Breach of Confidentiality, resulting in:
	Discomfort		Confusion	X	Invasion of privacy
	Serious Injury		Hallucination		Potential loss of employment or insurability
	Death		Stress		Potential criminal prosecution
	Injury from invasive medical procedure		Guilt		
	Harm from possible side effects from drugs		Loss of self-esteem		None (only applicable if all data is stripped of all identifiers and not coded)
X	Rare allergic reaction to radiologic contrast dye		Embarrassment		
	None	X	Possible anxiety or claustrophobia during MRI exam		
			None		

c) Describe the procedures or safeguards in place to protect against or minimize potential risks (e.g., referral to psychological counseling resources).

-Standard assessment of allergy or MRI-associated risk prior to MRI study

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-Standard care during phlebotomy
-Referral to psychological counseling if indicated

d) Who will be monitoring the risks noted above to ensure the safety of subjects?

X The Principal Investigator Describe your monitoring plan for reviewing interim results and/or safety concerns during the study:

-Contact with the volunteer prior to obtaining the MRI
-Post-procedural contact (after MRI and blood draw) to ascertain any concerns
-Contact information of PI will be made available to the volunteers

A group representing the study sponsor State name of group and describe monitoring plan for reviewing interim results and/or safety concerns during the study:

A Data Safety Monitoring Board (DSMB) State name of DSMB and describe procedures for submitting summary reports from the DSMB to the IRB:

Other:

If multi-site trial, are DSMB report(s) available for research already conducted?If yes, attach DSMB reports. (see clinical research glossary for "DSMB" clarification. If you think your study warrants DSMB oversight and you do not know of one to utilize, please contact the IRB office.)

e) Are there any stopping rules based on the risks noted above, or other study criteria? If yes, describe below and include study endpoints. (Click "Help" above for more information.)/ N

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* * * Benefits * * *

10. Benefits(This section is not enabled for exempt or cooperative studies)/

a) Are there any direct benefits to the research participants? Note: Direct benefit is a valued or desired outcome; an advantage (please do not include monetary inducement or compensation).If yes, please describe. N

b) Are there any anticipated benefits of this study to society, academic knowledge or both? If yes, please describe. Y

The results of this study should define the effectiveness of MRI and/or CPK / aldolase as diagnostic tools in future patients with suspected local anesthetic-induced myotoxicity

c) Explain how the potential benefits justify the potential risks involved in participation in this research.

For this previously unknown complication, new knowledge is critical for both understanding the proper diagnosis and for complication management. We have tried other routes to understand the diagnostic paradigm, to no avail. The low risk and inconvenience of postoperative MRI and CPK / aldolase studies will facilitate further knowledge related to this previously unknown complication.

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* * * Confidentiality * * *

11. Confidentiality

a) Which of the following types of data will be associated with this study. Consider all aspects of the

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study.(Click 'Help" above for more information)/

- [X] Identifiable
- [ ] Anonymous
- [X] De-identified
- [ ] Coded

b) Describe your protection method(s) in two or three sentences (e.g. coding system, limited access, password protected, certificate of confidentiality, etc.). Include safeguards to protect against direct or indirect identification of subjects in any reporting of research results (e.g. publications):

-MRIs contain patient names and medical record numbers will be seen by the blinded radiologist
-CPK reports contain patient names and medical record numbers, but will be seen only by Dr. Neal and the patient's orthopedic team
-A password-protected spreadsheet housed on a VMMC password-protected computer will be used to link MRN to radiologist-generated MRI standard reading and CPK levels
-MRNs will be removed from the spreadsheet prior to sharing with Dr. Steffel (at VA Puget Sound).
-Subject number, age, results of MRI and enzyme analysis, sex. No other identifiable information

c) Other than study staff and BRI Regulatory & Compliance, what entities will have access to research records and/or data that identify subjects (including coded data)?

NIH	Study Sponsor	Contracted monitor
FDA	Personal physician	[X] None

Other: (explain below)

d) How will research data be recorded?

Case report forms	Remote data entry (e.g. central database off site)	[X] Local database (e.g. Excel spreadsheet)
REDCap database	Patient medical records	N/A

Other: (explain below)

e) How will research records be stored locally?

[X] VMMC/BRI server	[X] Investigator's computer	Locked file cabinet
Locked office	N/A	Other: (explain below)

f) How will specimens be stored?

Limited access refrigerator / freezer	Locked cabinet / office
[X] N/A	Other: (explain below)

g) After completion of this study, will you keep any data and/or specimens for future research purposes? N

if yes then answer the following questions:Describe why the information and/or specimens will be retained (i.e., possible use for another research project[s], etc.). Note: Separate IRB applications must be submitted for additional use of retained data and/or specimens outside the approved protocol:

Describe in two or three sentences how the confidentiality of the retained information and/or specimens (whether directly identifiable or coded) will be maintained:

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h) Indicate the length of time research records and/or specimens will be kept before EITHER all identifiers/codes are removed OR the records and/or specimens are destroyed. Describe the procedures you will use.

Research records will be kept 1 year after publication of our results. After that, the spreadsheet will be turned over to BRI for archiving.

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* * * Consent Information * * *

12. Consent Information

Consent Instructions and Checklist

Template Consent Forms and Guidance

a) Click "Add" to enter information in the "Informed Consent" table below. This includes translated consents and waivers of consent. Exempt Studies: This table is disabled. If a consent is used then attach in the attachment section. Chart review: If accessing medical charts without consent, a waiver of consent is required. Oral Consent: A waiver of signed consent is required. Subjects under 18 yrs old: Go to the next section. complete and attach assent information. Enter information in the Informed Consent table separately for each consent and/or waiver of consent.

Informed Consent Table

Title	Consent Type
Clean Consent - Vers. 04.09.18 - IRB18-008	Consent
IRB Stamped Approved Consent - Vers. 04.09.18 - IRB18-008	Consent
Revised Consent 5.17.18	Consent
Consent 5.29.18 revision	Consent

Informed Consent Table

Title (e.g. main, screening, translated, oral, information sheet, waiver request) *	Clean Consent - Vers. 04.09.18 - IRB18-008		
Consent Information Type*	Consent		
Consent Document*	X	Attachment	Clean Consent - Vers. 04.09.18 - IRB18-008

Who will obtain subjects consent? (Check all that apply)

Principal Investigator
Co-Investigator
Study Coordinator
Research assistant(s)
Other research staff
Contracted Data Collection Firm
Other (please specify)

Informed Consent Table

Title (e.g. main, screening, translated, oral, information sheet, waiver request) *	IRB Stamped Approved Consent - Vers. 04.09.18 - IRB18-008		
Consent Information Type*	Consent		
Consent Document*	X	Attachment	IRB Stamped Approved Consent - Vers. 04.09.18 - IRB18-008

Who will obtain subjects consent? (Check all that apply)

X	Principal Investigator
X	Co-Investigator
	Study Coordinator
	Research assistant(s)
	Other research staff
	Contracted Data Collection Firm
	Other (please specify)

Informed Consent Table

Title (e.g. main, screening, translated, oral, information sheet, waiver request) *	Revised Consent 5.17.18		
Consent Information Type*	Consent		
Consent Document*	X	Attachment	Revised5.17.18.Consent Document - IRB18-008

Who will obtain subjects consent? (Check all that apply)

X	Principal Investigator
X	Co-Investigator
	Study Coordinator
	Research assistant(s)
	Other research staff
	Contracted Data Collection Firm
	Other (please specify)

Informed Consent Table

Title (e.g. main, screening, translated, oral, information sheet, waiver request) *	Consent 5.29.18 revision		
Consent Information Type*	Consent		
Consent Document*	X	Attachment	IRB18-008 Consent Document.Rev 5.29.18

Who will obtain subjects consent? (Check all that apply)

X	Principal Investigator
X	Co-Investigator
	Study Coordinator
	Research assistant(s)
	Other research staff
	Contracted Data Collection Firm
	Other (please specify)

If consenting human subjects answer the questions below. If NOT consenting human subjects, leave blank and skip to the next section.

b) Describe the process used to consent all subjects on the study.

-Volunteer subjects will be identified in orthopedic office by Dr. Verdin or his staff
-Those interested in participating will be consented by Joseph M. Neal, MD at least 24 hours prior to their surgery. If possible, consent will be obtained in person. If not possible, consent will be obtained via phone.

c) Will subjects have as much time as they want between the explanation of the study and signing the consent form? If no, or N/A explain below. Y

d) If consent is being obtained from non-English speaking subjects, explain the translation process for all documents seen by subjects, including consent documents. Describe the consent process in these circumstances.

N/A

e) Do you plan on having a Legally Authorized Representative (LAR) involved in the consent process? If yes, explain below and ensure the appropriate section is included in the consent form. N

f) Will you require an impartial third party witness be included in the consenting process? If yes, explain below and ensure the appropriate section is included in the consent form. N

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* * * Assent Background * * *

13. Assent Background (Continue to the next section if no subjects under the age of 18 will be enrolled in this study)

a) Complete the "Assent" table below. Attach assent documents and/or request assent waivers. Click "Help" above for more information regarding assent and assent waiver.

You must check children (under 18) on the Subject Checklist section to activate this table.

b) Complete the Regulatory Compliance worksheet below:

Regulatory Compliance - Subpart D - Children

Provide the specific age range for children (less than 18 years old) you wish to enroll in the study and what is your accrual goal:			
Age Range:		Total Accrual Goal:	
Check the appropriate box below (only one) to indicate which category your study may be approved in light of 45 CFR 46 subpart D for research involving children. Chlick on the links below for guidance.			
	Research not involving greater than minimal risk. 45 CFR 46.404		
	Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects. CFR 46.405		

	Research involving greater than minimal risk and no prospect of direct benefit to the individual child subjects involved in the research, but likely to yield generalizable knowledge about the subject's disorder or condition. 45 CFR 46.406
	Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. 45 CFR 46.407
	Will you be using an Assent Form? (Required for subjects 7-11 years old per BRI IRB policies - see 45 CFR 46.408 for reference)
Describe in the space below the details of your assent process for children in your study. (Include specific approach(es) to subjects in various age ranges, how assent will be documented, who will be able to give persimssion for each child (e.g. child's parent(s) or guardian), and how this permission will be recorded in the file.)	

	Does your study involve an FDA regulated drug, device, or biologic? If yes, check the appropriate box below (only one) to indicate which category your study may be approved in light of 21 CFR 50 Subpart D for research involving children. Click on the links below for guidance.		
	Clinical investigations not involving greater than minimal risk 21 CFR 50.51		
	Clinical investigations involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects. 21 CFR 50.52		
	Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects.		
	Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. 21 CFR 50.53		
	Will you be using an Assent Form? (Required for subjects 7-11 years old per BRI IRB policies - see 45 CFR 46.408 for reference)		

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* * * HIPAA * * *

14. Health Insurance Portability and Accountability Act (HIPAA)

If you are using PHI and this page is not active you must return to the General Checklist and check the box regarding the use of PHI in this research.

HIPAA Privacy Rule: Establishes the right of an individual to authorize a covered entity, such as health plan, health care clearinghouse or health care provider, to use and disclose his/her Protected Health Information (PHI) for research purposes. The Privacy Rule defines the elements of individual information that comprise PHI and establishes the conditions under which PHI may be used or disclosed by covered entities for research purposes. It also includes provisions to allow an individual's PHI to be disclosed or used in research without the person's authorization (i.e., IRB Waiver of HIPAA Requirement Authorization). For more information refer to the HIPAA Privacy Rule.

Protected Health Information (PHI):Health information with one or more of the identifiers listed below. For more information see the NIH website. Research which involves the use of de-identified data is exempt from HIPAA requirements. In order to be de-identified data NONE of the subject identifiers listed below can be collected, used, reviewed, recoded, accessed or disclosed.

For more information see the following:VM/BRI Protected Health Information Guidance Document

a) How will you obtain approval to access PHI for this research?

X HIPAA Authorization request from subject

X Incorporated into consent form Stand alone document

Waiver of Subject HIPAA Authorization (partial or complete)(complete question e. below)

Limited Data Set and Data Use Agreement

Other: (explain below)

c) Will any non-VM/BRI personnel need access to PHI? If yes, how and where will they access subject PHI (e.g. on-site, remote via Cerner, etc.)? N

d) Review the following list and indicate if any of the information will be collected from any medical records for the purpose of this research project.

Names

Social Security Numbers

Telephone Numbers

All geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code, if according to the current publicly available data from the Bureau of the Census;

i. The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and

ii. The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.

All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.

Fax Numbers

Electronic Mail Addresses (email)

X Medical Record Numbers

i. You must identify the data points being collected from MRN by attaching a separate data collection sheet or listing them in the procedures section.

Health Plan Beneficiary Numbers

Account Numbers

Certificate/License Numbers

Vehicle Identifiers and Serial Numbers, including License Plate Numbers

Device Identifiers and Serial Numbers

Web Universal Resource Locations (URLs)

Internet Protocol (IP) Address Numbers

Biometric Identifiers, including Finger and Voice Prints

Full Face Photographic Images and any Comparable Images

Any other unique identifying number, character, or code (note this does not mean the unique code assigned by the Investigator(s) to code the research data)

e) Are you requesting a HIPAA waiver? (Required for any type of waiver of consent)If yes, answer the following questions. If no, proceed to the next section. N

i. Explain why the research cannot reasonably be conducted without the waiver of authorization:

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ii. Explain why the research cannot reasonably be conducted without access to and use of identifiable health information:

iii. Describe the reasonable safeguards to protect identifiable information from unauthorized use or re-disclosure:

iv. Describe the reasonable safeguards to protect against identification, directly or indirectly, any patient in any report of the research:

v. Describe the plan to destroy the identifiers at the earliest opportunity consistent with the research. If there is a health or research justification for retaining identifiers, or if law requires you to keep such identifying information, please provide this information as well:

vi. Provide written assurance that identifiable information will not be reused/disclosed to any other person or entity, unless such use is required by law, for oversight of the research study, or for other research permitted by law:

vii. Explain why the research is of sufficient importance to outweigh the privacy intrusion:

viii. Explain who the subject should contact to enforce patient rights, or to obtain an accounting of the research disclosures (e.g. PI, sub-investigator, coordinator):

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* * * Drugs and Devices * * *

15. Drugs and Devices

a) Does this study involve a drug or device? If YES, continue below.If NO, proceed to the next section. Y

i) Is the drug(s) or device(s) FDA approved? If YES, list drug / device name and explain in text field below. (e.g. HDE, 510K, Compassionate Use, etc) If NO, click "add" and complete the table below for each investigational drug(s) or device(s). Y

MRI

(These tables are not activated unless a drug / device question is checked on the General Checklist section)

b) Briefly describe the drugs and devices listed above. Include any relevant information that has not been described in the protocol summary or background sections.

MRI will be used to obtain thigh scans

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* * * Potential Conflict of Interest * * *

16. Potential Conflict of Interest(This section is not enabled for exempt studies)/

a) Y Is there funding for this study?

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b) N If yes, are there any positive financial disclosures related to this study for any key personnel?

c) N Regardless of funding, are there any positive positional disclosures related to this study for any key personnel?

d) Y I attest that I have read the 'https://brinet.benaroyaresearch.org/center/Documents/VM%20Research%20Conflicts%20of%20Interest.pdf#search=research%20conflict'target='blank'VM Conflict of Interest Policy and agree to abide by its terms. I will update this protocol when new or changes in conflict of interest arise, and I will comply with any conflict management plan required by the Institutional Review Board (IRB) to manage, reduce, or eliminate any actual or potential conflict of interest for the duration of the research.

If Yes to b) or c) above, complete the table and answer the questions below concerning the potential conflict of interest. If No, then proceed to the next section.

Minimizing Risks and Disclosure to Subjects

e) N Have you disclosed any actual, potential or perceived conflicts of interest in the consent form? Research Personnel are required to disclose all such conflicts to all research participants in the research consent form.

f) What steps, if any, have you taken or will you take to manage the conflict of interest and minimize the risks associated with any actual, potential or perceived conflicts of interest arising out of this research?

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* * * Attachments * * *

17. Attachments

Attach relevant documents here. These could include:

- Collaborating Investigator's IRB approval and approved documents
- Conflict of Interest information
- Debriefing Script; Grant/Sub-contract
- HIPAA Authorization Form from HIPAA-covered entity
- Interview/Focus Group Questions
- Investigator's Brochure
- Letters of Agreement/Cooperation from organizations who will help with recruitment
- Questionnaires/Surveys
- Radiation Control Office approval material
- Recruitment Material (e.g., flyers, email text, verbal scripts)
- Protocol
- Patient Card
- Other files associated with the protocol (you can upload most standard file formats: xls, pdf, jpg, tif, etc.)

Please be sure to attach all documents associated with your protocol. Failure to attach the necessary files may result in this protocol being returned prior to review.

To update or revise any attachments, please delete the existing attachment and upload the revised document to replace it.

Select from list	Attachment Name	Attached Date	Submitted Date

Data Collection Sheet	IRB18-008 Copy of Study Data Sheet	03/08/2018	05/22/2018
Other	IRB18-008 Neal Financial Disclosure	03/08/2018	05/22/2018
Data Collection Sheet	IRB18-008 Copy of MRI Data Sheet	03/08/2018	05/22/2018
Protocol	Clean Protocol - Vers. 04.09.18 - IRB18-008	04/13/2018	04/13/2018
Protocol	IRB18-008 Protocol.Rev 5.29.18	05/29/2018	05/29/2018

* * * Obligations * * *

Note: The use of "I" below refers to the Principal Investigator (PI). If someone other than the PI is completing and submitting this application, that person is responsible to make sure the PI is aware of their obligation and assurances cited below. The PI is ultimately responsible for all conduct under this study and answers provided in this IRB submission.

Research Obligations of the Principal Investigator Include the Following:

Training - ALL key personnel, including any newly added personnel, must meet all IRB required training requirements (e.g. CITI Ethics, GCP, Conflict of Interest). Training refreshers must be completed at the appropriate intervals (i.e. every three (3) or four (4) years).

Study Modifications - Changes to any aspect of the study (e.g. protocol, consent/assent forms, advertising materials, additional key personnel, subject population, etc.) will be submitted to the IRB for approval before instituting the changes.

Final Report - The IRB will be notified when the study is complete, and must be closed out in eProtocol prior to expiration of the approval.

Investigator's Statement and Assurance of Confidentiality:

I certify that I have reviewed this application, including attachments, and all information contained herein is accurate to the best of my knowledge.

I agree to not enroll any subject(s) or collect any data intended only for research use prior to issuance of an IRB approval.

I understand that I am fully responsible for the execution and management of this study, and I am responsible for the performance of any sub-investigators or key personnel, including their adherence to all of the applicable policies and regulations.

I agree to report any substantive changes to the information contained in this application, unanticipated problems, or adverse events encountered during the project immediately to the IRB.

I will ensure the names of any human subjects or any identifiable data from human subjects shall be treated as confidential information. This information will not be disclosed to anyone other than those directly connected with the research project unless the patient has given prior approval in writing.

If this is a funded project, I certify that the funding source document is entirely consistent with the corresponding study protocol.

I certify I have not been barred from doing research by any regulatory agency or entity. If I am a physician (or other licensed health care professional), I certify that my medical (or other) license is current.

I further agree any failure to perform the undertaking specified above shall be good cause for termination of the research project.

When Closing Your Protocol:

I understand when I close this protocol with the IRB NO further data collection, follow-up with subjects, coding of data, data analysis, and manuscript preparation that requires personal identifiable information (e.g. PHI) may be conducted.

I agree to retain all research materials for at least 10 years after closure of the research project and acknowledge these documents may be subject to review by the Clinical Research Program and IRB, if deemed necessary.

I further certify I will not take any PHI and/or specimens generated from this research with me if I leave BRI/VM, unless having first established an agreement with VM legal in advance of my departure.

I confirm this study will not begin until the investigator receives written final approval or determination of exemption.

X The Principal Investigator has read and agrees to abide by the above obligations.

Continuing Review - You are responsible to complete and submit a Continuing Review form at least 30 days prior to the date of expiration. You will be asked to note accomplishments of your project at that time.

Protocol Deviations/Violations, Adverse Events (AEs) that occur in the course of the protocol will need to be submitted in a prompt manner from when they occurred.

X The Principal Investigator has read and agrees to abide by the above obligations.

Please click "next" to continue to protocol Check for Completeness. If the protocol is complete and ready for submission, please click "Submit Form" to your left to submit your protocol for IRB Review.

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* * * Event History * * *

Event History

Date	Status	View Attachments	Letters
05/29/2018	AMENDMENT 2 FORM SUBMITTED	Y	
05/29/2018	AMENDMENT 2 FORM CREATED		
05/24/2018	AMENDMENT 1 FORM APPROVED	Y	Y
05/23/2018	AMENDMENT 1 FORM REVIEWER(S) ASSIGNED		
05/22/2018	AMENDMENT 1 FORM SUBMITTED	Y	
05/17/2018	AMENDMENT 1 FORM CREATED		
04/30/2018	NEW FORM APPROVED	Y	Y
04/30/2018	NEW FORM UNDO APPROVED		
04/30/2018	NEW FORM APPROVED	Y	Y
04/17/2018	NEW FORM REVIEWER(S) ASSIGNED		
04/13/2018	NEW FORM REVIEWER(S) ASSIGNED		
04/12/2018	NEW FORM PANEL MANAGER REVIEW		
03/08/2018	NEW FORM PANEL ASSIGNED		
03/08/2018	NEW FORM SUBMITTED	Y	
01/26/2018	NEW FORM CREATED		