NCT number: NCT04051242

Official Title: XENMATRIX™ AB Surgical Graft for the repair of severe musculotendinous tissue damaged by trauma.

Study Protocol Document Date (Study IRB closure date): February 13, 2024

Study Consent Document Date (last IRB approved): May 9, 2023

University of Pittsburgh | Institutional Review Board
Office of Research Protections

STUDY CLOSURE

Date:	February 13, 2024
IRB:	CR19040344-023
PI:	J. Peter Rubin
Title:	XENMATRIX™ AB Surgical Graft for the repair of severe musculotendinous tissue damaged by soft tissue trauma
Funding:	Name: U.S. Department of Defense (DoD), Grant Office ID: pending, Funding Source ID: Pending
IRB Coordinator:	Kathleen Hurst

The Institutional Review Board acknowledges your request for closure of the above referenced protocol effective as of 2/13/2024. As part of this action:

- The protocol is permanently closed to enrollment.
- All subjects have completed all protocol-related interventions.
- Collection of private identifiable information is completed.
- Analysis of private identifiable information is completed.

It is the responsibility of Principal Investigator to notify all members of the research team of this action.

If you have any questions, please contact the University of Pittsburgh Human Research Protection Director, Jean Barone, at (412) 383-1480 or email baronej2@pitt.edu.

Please take a moment to complete our Satisfaction Survey as we appreciate your feedback.

PittPRO | Pitt Protocol Review Online

Date: Wednesday, February 14, 2024 9:23:06 AM

Print Close

View: Pitt SF: Basic Study Information 8.2

Basic Study Information

1. * **Title of study:**
   XENMATRIX™ AB Surgical Graft for the repair of severe musculotendinous tissue damaged by soft tissue trauma

2. * **Short title:**
   Enhanced Bioscaffold for Volumetric Muscle Loss

3. * **Brief description:**
   Previously, our group conducted a human subject clinical trial (NCT01292876, PRO10010500) to evaluate a regenerative medicine approach using ECM (extracellular matrix) for VML (volumetric muscle loss) treatment [Dziki et al., 2016, Han et al., 2016]. ECM scaffolds were implanted and combined with aggressive and early physical therapy in 13 subjects, then followed for 24-28 weeks after implantation. Histomorphological assessments collected from core needle biopsies identified formation of new, vascularized, innervated islands of skeletal muscle within the implantation site. Subjects demonstrated increased force production in physical therapy evaluations and improved functional task performance when compared with pre-operative performance. By 6 months after ECM implantation, subjects had a 37.3% improvement in strength and 27.1% improvement in range-of-motion tasks. Additionally, changes in nerve conduction study (NCS) and electromyography (EMG) before and after ECM implantation were measured. 63% of study participants experienced improvements in NCS or EMG within the scaffold remodeling site, indicating clinical improvement in muscle strength. The promising functional and regenerative results from this early study encourages evidence of ECM bioscaffolding as a viable treatment to VML.
   We propose in this project to use XENMATRIX™ AB Surgical Graft which has 510(k) approval [#K162193] intended for implantation to reinforce soft tissue where weakness exists and for surgical repair of damaged or ruptured soft tissue, including abdominal plastic and reconstructive surgery; muscle flap reinforcement; hernia repair including abdominal, inguinal, femoral, diaphragmatic, scrotal, umbilical, and incisional hernias. The graft has an antibiotic coating, specifically, Rifampin and Minocycline. This coating has been shown in preclinical in vitro and in vivo testing to reduce or inhibit microbial colonization on the device. The claim of reduction of bacterial colonization of the device has not yet been established with human clinical data, nor has a clinical impact associated with this claim been demonstrated and will need further investigation. This trial proposes to test the applicability and utility of XENMATRIX™ AB Surgical Graft in the restoration of function in the setting of volumetric muscle loss after trauma. 10 subjects will be enrolled for participation in the study. Prior to Graft implantation, subjects will receive a pre-operative course of physical therapy for a maximum time period of 16 weeks. A physical therapist will

confirm that functional plateau is reached prior to implantation of the Graft. Following Graft implantation, radiographic, functional, and electrophysotherapy outcomes will be measured at various time points up to 22-30 weeks post-operatively. A CT scan or MRI will be collected at the screening visit to evaluate tissue volume, then again at post-operative Visit 5. Physical therapy training will be performed as a research procedure following Graft implantation for a maximum of 30 weeks. Additionally, physical therapy evaluations will be conducted at screening, pre-op visit 1, post-op visits 1, 2, 3, 4 and 5. A small core needle biopsy 1-5 grams will be collected at three time points to conduct histomorphological assessment of the tissue prior to graft implantation (Operative visit, Visit 3 and at Visit 5).

4. * **What kind of study is this?**
Single-site study

5. * **Will an external IRB act as the IRB of record for this study?**
Yes **No**

6. * **Local principal investigator:**
J. Peter Rubin
* **Is this your first submission, as PI, to the Pitt IRB?**
○ Yes ○ No

7. * **Does the local principal investigator have a financial interest related to this research?**
○ Yes ◉ **No**

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

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

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

Funding Sources

1. * **Indicate all sources of support:**
   External funding

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

Funding Source	Sponsor's Funding ID	Grants Office ID	Attachments	Pitt Awardee	Grant Recipient
U.S. Department of Defense (DoD)	Pending	pending	MTEC VML project documents		

View: Pitt SF: Study Team Members

Study Team Members

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

Name	Roles	Department/School	Affiliation	Involved in Consent	Qualifications	Financial Interest
Fabrisia Ambrosio	Co-investigator	U of Pgh | School of Medicine | Physical Medicine and Rehabilitation	Pitt faculty	no	Fabrisia Ambrosio, PhD, MPT, Director of Rehabilitation for UPMC International and Associate Professor in the Departments of Physical Medicine and Re... view all	no
Stephen Badylak	Co-investigator	U of Pgh | School of Medicine | Surgery	Pitt faculty	no	Stephen Badylak, DVM, PhD is a Professor in the Department of Surgery, a Deputy Director of the McGowan Institute for Regenerative Medicine (MIRM), a... view all	no
Michael Boninger	Co-investigator	U of Pgh | School of Medicine | Physical Medicine and Rehabilitation	Pitt faculty	no	Michael Boninger, MD is Professor in the Department of Physical Medicine & Rehabilitation at the University of Pittsburgh, fellowship in rehabilitati... view all	no
Matthew Bottegal	Co-investigator	U of Pgh | School of Medicine | Orthopaedic Surgery	Pitt staff	no	Matthew Bottegal, BS, Department of Plastic surgery. Mr. Bottegal has more than 15 years of experience as a research coordinator in multiple	no

Name	Roles	Department/School	Affiliation	Involved in Consent	Qualifications	Financial Interest
					discipli... view all	
Jeffrey Gusenoff	Co-investigator	U of Pgh | School of Medicine | Plastic Surgery	Pitt faculty	yes	Jeffrey Gusenoff, MD Associate professor in the Department of Plastic surgery. He is Board certified in plastic surgery and an expert in the areas o... view all	no
Armando Herradura	Co-investigator	U of Pgh | School of Medicine | Radiology	Pitt faculty	no	Armando Herradura, MD, Department of Radiology, currently in fellowship in musculoskeletal imaging and intervention at UPMC. As a board certified rad.. view all	no
Scott Johnson	Co-investigator	U of Pgh | School of Medicine | McGowan Inst Regenerative Med	Pitt staff	no	Scott holds a Master's degree in Science with an emphasis on the evolution of behavior and over 20 years research experience in hematology and regene... view all	no
Roy Kazan	Co-investigator	Other	UPMC resident/fellow	yes	Dr. Roy Kazan is a licensed physician and a resident within the department of plastic surgery. He will be involved in consent, screening, medical rec... view all	no
Lauren Malacarne	Co-investigator	U of Pgh | School of Medicine | Physical Medicine and Rehabilitation	UPP/UPMC staff	no	Lauren Malacarne PT DPT is a physical therapist working at	no

Name	Roles	Department/School	Affiliation	Involved in Consent	Qualifications	Financial Interest
					UPMC Mercy as an acute care physical therapist as well as the inpatient rehabilitation uni... view all	
Rebecca Parsons	Co-investigator	Other	UPP/UPMC staff	yes	Rebecca Parsons is a certified physician's assistant and will serve as Dr. Rubin's clinical designee on this study. She will be involved in screenin... view all	no
J. Peter Rubin	Principal Investigator	U of Pgh | School of Medicine | Plastic Surgery	Pitt faculty	yes	J. Peter Rubin, MD, Founding Chair of the Department of Plastic Surgery at the University of Pittsburgh, is the principal investigator. Dr. Rubin has... view all	no
Eleanor Shirley	Primary Study Coordinator Co-investigator	U of Pgh | School of Medicine | Surgery	Pitt staff	yes	Eleanor Shirley, M.A. Ms. Shirley has 20 years of experience at the University of Pittsburgh as a study coordinator, focused on surgical outcomes an... view all	no
Patsy Simon	Co-investigator	U of Pgh | School of Medicine | Plastic Surgery	Pitt staff	yes	Patsy Simon, BS, RN, CCRC, CCRA, ACRP-PM Director, Regulatory and Clinical Affairs for the UPMC Center for Innovation in Restorative Medicine,	no

Name	Roles	Department/School Affiliation		Involved in Consent	Qualifications	Financial Interest
					Depart... view all	
Abigail Skeel	Secondary Study Coordinator	U of Pgh | Student Affairs	Pitt staff	yes	Abigail Skeel BS, BA, is a clinical research coordinator within the department of plastic surgery. She has completed the departments' training and sh... view all	no
Mario Solari	Co-investigator	U of Pgh | School of Medicine | Plastic Surgery	UPP/UPMC staff	yes	Dr. Mario Solari, MD is employed by UPMC and a member of the Department of Plastic Surgery. As a Co-Investigator on this project he will provide clin... view all	no
Elizabeth Stanley	Co-investigator	UPMC | Hospital Divisions | Mercy	UPP/UPMC staff	no	Liz Stanley PT DPT is a physical therapist working at UPMC Mercy as an acute care physical therapist as well as the inpatient rehabilitation units. ... view all	no
Neill Turner	Co-investigator	U of Pgh | School of Medicine | Surgery	Pitt faculty	no	Dr. Neill Turner is a Research Assistant Professor in the Department of Surgery at the University of Pittsburgh. He earned his Bachelor's in Biomedic... view all	no
Yadira Villalvazo	Co-investigator	Other	UPMC resident/fellow	yes	Yadira Villalvazo, MD is a resident within the	no

Name	Roles	Department/School	Affiliation	Involved in Consent	Qualifications	Financial Interest
					department of plastic surgery. She will be involved in screening, medical record review, collection... view all	
Lynn Worobey	Co-investigator	U of Pgh | School of Engineering | Bioengineering Program	Pitt faculty	no	Lynn Worobey, PhD, DPT, ATP is a research assistant professor in the Department of Physical Medicine and Rehabilitation at the University of Pittsbur... view all	no

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

Name	Description
There are no items to display	

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

* ◉ Yes ○ No

View: Pitt SF: Study Scope 8.1

Study Scope

Check all that apply

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

2. * **Will any Waivers be requested?**
   - ☐ Waiver/Alteration of Consent
   - ☐ Waiver to Document Consent
   - ☐ Waiver/Alteration of HIPAA
   - ☐ Exception from consent for emergency research
   - ☑ N/A

3. * **Will this study involve any of the following?**
   - ☑ Specimens
   - ☐ Honest Broker to provide data/specimens
   - ☐ Return of Results to Subjects or Others
   - ☐ Fetal tissue
   - ☐ N/A

4. * **Will Protected Health Information be collected?**
   - ☐ Pitt medical records
   - ☑ UPMC medical records
   - ☑ Other Institutions' medical records
   - ☐ N/A

5. * **Other Requests?**
   - ☐ Deception (if not Exempt, also requires Waiver/Alteration of Consent)
   - ☐ Emergency Use / Single Patient Expanded Access (using FDA Form 3926)

- ☐ Placebo Arm
- ☐ Withdraw from usual care
- ☑ N/A

6. * **Determining Scientific Review:**
Department Scientific Review (this option MUST be picked if there is DoD funding)
* **Choose the appropriate organization to conduct the scientific review:**
U of Pgh | School of Medicine | Surgery | Plastic Surgery

7. * **Has this study (or substantially similar study) been previously disapproved by the Pitt IRB or, to your knowledge, by any other IRB?**
○ Yes ◉ **No**

Review the HRPO policy, if participating in research at the VA Pittsburgh Healthcare System or using funding from the VA

8. * **Does the study use an approved drug or biologic, use an unapproved drug or biologic, or use a food or dietary supplement to prevent, diagnose, cure, treat, or mitigate a disease or condition?**
○ Yes ◉ **No**

9. * **Does the study evaluate the safety or effectiveness of a device (includes in-vitro laboratory assays)?**
◉ **Yes** ○ No

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

○ Yes ◉ **No**

11. * **Does your research protocol involve the evaluation or use of procedures that emit ionizing radiation and, after reviewing this** HUSC guidance, **does your research protocol require HUSC review? (If yes, upload the** HUSC form **in the Local Supporting Documents section). If you are unsure of review requirement, select yes.**
○ Yes ◉ **No**

Research Sites

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

*** Select the UPMC sites where research will be conducted:**
Magee Women's Hospital
Montefiore
Presbyterian
Shadyside
Other UPMC Site- Specify below:

List the Other UPMC sites:

Department of Plastic Surgery Aesthetics Center: Isaly Building

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

The PI has adequate space for storing data to maintain the confidentiality for the participants of this study and we do not anticipate any issues with the availability of resources or the adequacy of the facilities to meet the needs for this clinical study. UPMC facilities have the resources and adequate space with which to conduct the research activities, allowing for space appropriate for the disclosure of private information (e.g., interview or exam room). There are adequate safeguards for the research staff and participants within the facilities and ability to handle emergency situations should they arise. UPMC Operative suites and clinics provide the support necessary to perform surgical procedures to meet the collection of data to assess the objectives of the study. The personnel are professionally qualified (licensed) and appropriately trained in responsible research conduct and Good Clinical Practice to ensure the safety to the human subject and maintain the integrity of the data collected. The research staff and licensed personnel are fully knowledgeable of the UPMC facility policy and procedures associated with the conduct of this study and necessary to meet the needs of this patient population.

View: Pitt SF: Devices

Devices

1. * **List each device in the study that will be evaluated for safety or effectiveness:**

	Device	Purpose	Type	Attachments
View	XENMATRIX AB™	This trial proposes to test the applicability and utility of XenMatrix™ AB Surgical Graft in the restoration of function in the setting of volumetric muscle loss after trauma. We propose to use XenMatrix™ AB Surgical Graft 510(k) approval [#K162193] intended for implantation to reinforce soft tissue where weakness exists and for surgical repair of damaged or ruptured soft tissue, including abdominal plastic and reconstructive surgery; muscle flap reinforcement; hernia repair including abdominal, inguinal, femoral, diaphragmatic, scrotal, umbilical, and incisional hernias. The graft has an antibiotic coating, specifically, Rifampin and Minocycline. This coating has been	Exempt from IDE requirements	XENMATRIX AB™ 510K Xen AB IFU_4.30.2019.pdf

Device	Purpose	Type	Attachments
	shown in preclinical in vitro and in vivo testing to reduce or inhibit microbial colonization on the device. The claim of reduction of bacterial colonization of the device has not yet been established with human clinical data, nor has a clinical impact associated with this claim been demonstrated and will need further investigation.		

2. **If applicable, identify each investigational device exemption (IDE) number:**

IDE Number	IDE Holder	Other Holder
There are no items to display		

3. **Attach files:** (attachments may include justification of risk determination, FDA correspondence and if the holder of the IDE is a University of Pittsburgh based, sponsor-investigator, attach both the FDA acknowledgement letter and approval letter)

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

4. * **Describe your plan to manage devices so that they will be used only on subjects and be used only by authorized investigators:**

There will be appropriate processes surrounding the product accountability of this device as it relates to the chain of custody, shipment, storage and record keeping controls regarding the device for this research project. The device will be shipped and stored per manufacturer instructions in original sealed packaging and stored separate from any other devices used in standard clinical care. The device will be stored within the controlled confines of the research center, under appropriate chain of custody and identified as a research device located within a container clearly marked with the study ID and PI name with contact information maintained behind double locked system. A device product accountability log will be maintained for this device and will be used to sign out the device for subject use. It will also identify and denote the receipt date, handling, storage, and maintenance information within this binder/ storage container. Only surgeon, MD Investigators, trained in the proper

grafting of the Bard XENMATRIX AB™ under this protocol will implement the surgery procedure for the subjects on this study.

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

Recruitment Methods

*** Will you be recruiting individuals for participation in this study?**
● **Yes** ○ No

1. *** Describe who will be recruiting individuals for participation for this study:**
Investigators and research staff will perform the recruitment activities to engage interest for participation within this patient population for this study. Research coordinators assist utilizing a script to conduct telephone screening activities. Should the potential candidate pass this process then the coordinator will discuss findings with the Investigator to bring potential study participants into the center to perform the screening visit.

2. *** Select all methods to be used for recruitment:**
Flyers/Posters or Brochures
Pitt+Me
Telephone scripts
Website/Social Media
Other

*** Enter description of 'Other' method of recruiting:**
The University of Pittsburgh, School of Medicine (Dr. Peter Rubin, MD) established a memorandum of understanding in October 2018 with military leaders from the Naval Medical Center San Diego (CAPT Craig Salt, MD - Plastic Surgeon) who lead the DoD-wide Project CARE (Comprehensive Aesthetic Recovery Effort) program. The Project CARE Mission is to improve the appearance and function of traumatically injured service members through aesthetic treatments and reconstructive surgery. The initial introduction is from the CARE physician or clinical care team who is known to the potential participant and should the patient want to inquire further, a referral to Dr. Rubin for a more comprehensive introduction to the study is completed. The research team will coordinate with Project CARE leaders, when possible, for subject recruitment of service members for the ten patient cohort study.

3. *** Provide details on your recruitment methods:**
Some potential subjects military and civilian will be recruited using advertisement (See Attachments) to be placed throughout the Oakland and greater Pittsburgh area via our existing contacts with military and civilian support groups, Plastic surgery clinics/Physician's offices local and national and throughout the University of Pittsburgh Medical Center facilities who treat potential trauma subjects who may meet the study eligibility criteria. Potential subjects will be identified through the registration of this study with the CTSI Research Participant Registry, clinical trials.gov, the UPMC Center for Innovation in Restorative Medicine (CIRM) website, and through postings within the military community (active commission and retired). If the potential subject is responding to an advertisement /posting within a military web-based network or through the above mentioned sources, the potential subject is

requesting to be evaluated for the purpose of participation in this study and no records are reviewed prior to study consent or registry consent being obtained.The potential subject will call the research coordinator in response to the advertisement. The research coordinator, utilizing a telephone script will obtain and document into the research binder, the verbal consent of the potential subject for participation for the pre-screening activity. The research coordinator will only pre-screen potential subjects for eligibility criteria by phone. The research coordinator will also obtain information specific to the registration of the potential subject for the screening visit. If the potential subject meets this criteria their information will be reviewed with the PI for further action. The PI will make a final determination on continuing the evaluation process and the potential subject will be contacted for further coordination of a screening visit.It is common practice for other plastic surgeons and physicians to refer patients to Dr. Rubin at this tertiary care center. Dr. Rubin, through clinical conferences and discussions with a variety of clinical services and referral sources, has facilitated awareness of this study. If the potential subject is referred to Dr. Rubin's practice for participation for this study, the initial introduction is from the SOC physician or clinical care team who is known to the potential participant. If the patient wants to inquire further, a referral to Dr. Rubin for a more comprehensive introduction to the study is completed. The introduction of the study is documented in the medical record of the primary practice. Medical records may be sent from the referring MD, by the potential candidate prior to the visit, or hand carried by the patient for Dr. Rubin's review at the time of the potential subject's visit. In order to limit the risk of exposure to Covid-19 through travel, if records and available and sent prior to the visit (CT scan/EMG nerve conduction tests done within the last year), the study physicians will review them prior to the screening visit for eligibility, to limit ineligible candidates travel risk. Private health information of subjects who undergo phone screen who do not proceed to signing study consent will be not be stored.

Study team members will be posting the Twitter/Facebook content

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

Study subjects will be reimbursed for their participation in the research study on a per diem total rate of $104.00 per visit, excluding mileage reimbursement. Per diem payment $104.00 per visit during subject surgery hospitalization will occur only up to the first 48 hours. This payment is intending to cover expenses (i.e. meals, parking, post-operative meds, tolls, etc.) which may be encountered and could be associated with the participation in this clinical trial. Subjects will receive mileage reimbursement per federal rate 0.58 / per mile round trip for all travel to research visits when using their own transportation. The subjects will receive the payment at the time of study visit completion for those performed at the University of Pittsburgh Medical Center. Physical therapy training session reimbursement will be provided at $20.00 /week, provided you complete the total weekly visits as ordered by the MD. No partial reimbursement will be provided for missed or incomplete weekly visits. Proper supporting documentation for mileage reimbursement is demonstrated by trip tickets or an internet map search inquiry from your place of residence to the study site displaying round trip mileage. Per visit travel may include air fare coverage round trip booked through the University of Pittsburgh travel agency from the

subject's place of residence to the UPMC Aesthetic Plastic Surgery Center or UPMC hospital/facility in lieu of round trip mileage. The subject will be reimbursed with the per diem rate using the UPMC "Vincent" system at the time of each visit.All participant reimbursement will be provided through Vincent Payment Solutions processing. The details of reimbursement will vary from person to person and will be discussed at time of consenting process.

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

	Document	Category	Date Modified	Document History
View	VML Recruitment Flier with tear offs 11.21.2022.doc(1)	Recruitment Materials	11/21/2022	History
View	VML Recruitment flyer with MD photos 11.21.2021.pdf(2)	Recruitment Materials	11/21/2022	History
View	Military Personnel Advertise - 11.21.20222.docx(2)	Recruitment Materials	11/21/2022	History
View	VML Phone Script V4.0(4)	Recruitment Materials	7/20/2020	History
View	STUDY19040344 Rubin.pdf(0.01)	Recruitment Materials	2/28/2020	History
View	TWEETS_social media(0.06)	Recruitment Materials	9/4/2019	History
View	Website tool9.3.2019_Version_0.01.pptx(0.04)	Recruitment Materials	9/3/2019	History

Study Aims

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

The purpose of this study is to prospectively evaluate functional improvement and tissue changes on a macroscopic and histological level after implantation of XENMATRIX AB™ Surgical Graft during musculotendinous unit repair in subjects with soft tissue injury and loss of skeletal muscle.

The primary objective of the study is to assess the ability of XENMATRIX AB™ Surgical Graft to restore both function and mechanical strength.

The secondary objectives are 1) to assess the rate of infection in the use of the XENMATRIX AB™ Surgical Graft and 2) to examine the histologic properties of the biopsy tissue material in each subject for future correlation with clinical outcomes.

We hypothesize that, in addition to providing mechanical strength, the XENMATRIX AB™ Surgical Graft will serve as a scaffold into which host cells and blood vessels will grow. As the implant material becomes vascularized, it will maintain long-term mechanical strength. The Graft will be able to withstand stress and potentially allow for adjacent muscle fibers to extend into the implant material as demonstrated by histomorphological assessment.

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

Volumetric muscle loss (VML) is a severe and debilitating issue which is generally caused by trauma such as battlefield injuries, degenerative diseases, or tissue resection [Grogan et al., 2011]. Current clinical standards of care to address VML include physical therapy or use of orthotics – neither of which correct the underlying strength deficits – and surgical tendon transfers or muscle transfers, which result in donor site morbidity and do not restore function [Lin et al, 2007]. Recently, the use of biologic scaffolds composed of extracellular matrix (ECM) has been evaluated as a treatment option for VML [Sicari et al., 2012, Sicari et al., 2014]. ECM is formed by secreted products of resident cells in every tissue and organ, it provides a mechanical framework for structural support and an inductive substrate for modulating cellular responses. ECM scaffolds are made by several commercial manufacturers and have been used for a variety of reconstructive surgical procedures for years. ECM implant materials for soft tissue repair are approved by the FDA and have a long track record in clinical surgery. They are composed of decellularized tissues and have been found to reinforce soft tissue where weakness exists, specifically for the reinforcement of soft tissue repaired by sutures or suture anchors during tendon repair surgery, including reinforcement for the rotator cuff, patella, Achilles, biceps, quadriceps, and other tendons [Agrawal et al., 2009].

Previously, our group conducted a human subject clinical trial (NCT01292876,

PRO10010500) to evaluate a regenerative medicine approach using ECM for VML treatment [Dziki et al., 2016, Han et al., 2016]. ECM scaffolds were implanted and combined with aggressive and early physical therapy in 13 subjects, then followed for 24-28 weeks after implantation. Histomorphological assessments collected from core needle biopsies identified formation of new, vascularized, innervated islands of skeletal muscle within the implantation site. Subjects demonstrated increased force production in physical therapy evaluations and improved functional task performance when compared with pre-operative performance. By 6 months after ECM implantation, subjects had a 37.3% improvement in strength and 27.1% improvement in range-of-motion tasks. Additionally, changes in nerve conduction study (NCS) and electromyography (EMG) before and after ECM implantation were measured. 63% of study participants experienced improvements in NCS or EMG within the scaffold remodeling site, indicating clinical improvement in muscle strength. The promising functional and regenerative results from this early study encourages evidence of ECM bioscaffolding as a viable treatment to VML. We propose to test the applicability and utility of XenMatrix™ AB Surgical Graft in the restoration of function in the setting of volumetric muscle loss after trauma.

XENMATRIX™ AB Surgical Graft, an acellular, sterile, non-pyrogenic porcine dermal matrix, comprised predominantly of water and collagen, coated with antibiotics, specifically, Rifampin and Minocycline. This graft is made from the same species (porcine) and organ (SIS) as the ECM scaffold evaluated in the study referenced above. However, the ECM scaffold in the previous study did not contain an antibiotic coating. We hypothesize that incorporation of antibacterial coating will decrease chronic inflammation at the site of implantation, eliminating biofilm formation and, thus enhancing range-of-motion and, ultimately result in promising functional improvements.

XENMATRIX™ AB Surgical Graft is packed hydrated in sterile saline for use in the reconstruction of soft tissue deficiencies and will be supplied in a single sheet or strand configuration in sterile form in a sealed double pouch system of sizes ranging from 150cm² to 665cm². Intended use is for implantation to reinforce soft tissue where weakness exists and for surgical repair of damaged or ruptured soft tissue, including plastic and reconstructive surgery; muscle flap reinforcement; hernia repair including abdominal, inguinal, femoral, diaphragmatic, scrotal, umbilical, and incisional hernias. As listed in the FDA 510k approval and IFU, this device provides "a remodelable scaffold that is replaced by the patient's own soft tissues." Data to support the use of this device for tendon repair was evaluated by the FDA, and approval granted (510(k) #K162193 (attachment) in 2016. We are using this device consistent with the FDA-approved indications and measuring outcomes over a 6 month time period.

Study Design

1. **Total number of subjects to be enrolled at this site (enter -1 for chart reviews, banking, registries):**
30

2. **Describe and explain the study design:**
This is a prospective, single center study conducted at the University of Pittsburgh designed to test the applicability and utility of XenMatrix™ AB Surgical Graft in the restoration of function in the setting of volumetric muscle loss after soft tissue trauma. Plan is to enroll up to 30 subjects to have 10 undergo study surgical intervention.

3. **Describe the primary and secondary study endpoints:**
Primary endpoints:
1.) Assessment of patient extremity function and mechanical strength post implantation of XENMATRIX AB™ Surgical Graft; after skeletal muscle injury.

Secondary endpoints:
1. Patient rate of infection with the use of XENMATRIX AB™ Surgical Graft;
2. Examination of histological properties of the biopsy tissue material in each subject for future correlation with clinical outcomes.

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

Duration of an individual subject's active participation:
The duration of study participation is approximately 9-11 months
Duration anticipated to enroll all subjects:
21-22 months
Estimated date for the investigator to complete this study (complete primary analyses):
7/31/2021

5. **List the inclusion criteria:**
- Age: 18 to 70 years of age and able to provide informed consent

- Civilian, and current or former military personnel are eligible to participate

- Have suffered injury resulting in a structural deficit of a minimum of 20% of the muscle group mass, as determined by CT/MRI and EMG/NCV and a functional deficit of a minimum of 25%, as determined by Physical Therapy when compared to a contralateral limb present; or if bilateral injury is present to extremities, the potential surgical extremity is to be compared against normal expected values of a sample population of similar age and gender and evidence of remaining tendon and musculotendinous units that could be surgically repaired with sutures.

• Injuries may encompass a single muscle belly or compartment, whether an area is expected to be repaired by sutures will be determined from imaging studies and physical examination. Muscle groups which originate or attach to the long bones of the extremity, and which directly affect strength and function (i.e., Pectoralis Major, Coracobrachialis, Subscapularis, Teres Major/Minor, Latissimus Dorsi, Supraspinatus, Infraspinatus, Gluteus group, Tensor fasciae latae, Piriformis, and quadratus femoris) will also be included in this clinical trial.

• Have suffered traumatic injury within the last 18 months to the upper and/or lower extremity; Target of 18 months or less but subject's may be enrolled with injury outside this range if the principal investigator determines that there is viable muscle in the injured compartment determined by clinical exam and imaging studies.

• Eligible for study procedures 3 months post injury with stability determined by the Principal Investigator and/ or Physician Co-Investigator

• Without a diagnosis of diabetes, or with well controlled diabetes as determined by physician discretion and with documentation of an HbA1c result of 8.0 or less within the past three months

• Willing and able to comply with follow up examinations, radiographic studies, physical therapy, muscle biopsy and laboratory tests.

5. **List the exclusion criteria:**

• Inability to provide informed consent

• Poor nutrition (demonstrated by clinically significant abnormal lab results for serum albumin and pre-albumin values, per the investigator's discretion)

• Chronic disease such as congestive heart failure, liver disease, or renal disease.

• Active and unstable disease state or infection anywhere in the body per Physician's evaluation and determination (demonstrated by stated or medical record history and abnormal lab range for CBC with Differential and Platelet, Liver function and chemistry panel values)

• Known coagulopathy (demonstrated by stated or medical record history of diagnosis)

• Pregnancy (demonstrated by a positive result of a urine pregnancy test)

• Diagnosis of cancer within last 12 months and /or actively receiving chemotherapy or radiation treatment

• Subjects with an Axis I diagnosis DSM-IV (e.g. for example, Schizophrenia, Bipolar

Disorder). Subjects who are found to be stable on medication and receive psychiatric clearance could be eligible for study participation per the Physician's discretion

• Subjects with complete muscle/tendon gaps greater than 5 cm that are obvious on imaging studies and are unlikely to be reasonably repaired with sutures and reinforcement, and will be excluded. The investigators recognize that these findings may not be clear on imaging studies, and that the clinical judgment of the surgeon shall be applied in each case.

• Subjects with a known hypersensitivity to porcine serum products

• Allergies to the antibiotics, Rifampin, minocycline, tetracycline currently associated with the XENMATRIX™ AB Surgical Graft

• Any condition or situation as it relates to the subject's health or safety, that would render concern to the investigators, and therefore preclude subject enrollment in the study.

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

● **Yes** ○ No

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

This is a DOD contract awarded to the University of Pittsburgh and Dr. Rubin. This study is for the advanced medical research, development of available technologies, efficacy studies and completion of required FDA trials, to treat wounded personnel who have suffered burn and blast injuries. Military and civilian populations who are considered adults and do not consist of anyone under the age of 18 years will only be considered for participation in this clinical trial.

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

This is a pilot study in which the results of the structural and functional evaluation will be compared within each subject from the preoperative values to the 6 month post operative time values. Since each subject will have different pathology, a different size and shape of the defect, and varying length of time from the initial injury, traditional statistical analysis will not be possible between individual subjects. Therefore, the potential benefit will be evaluated for each subject individually. If possible, a comparison of the percent change from preoperative values to the postoperative values will be determined as a group (n=10). However, the potential confounding variables and limitations of this type of study must be recognized.

View: Pitt SF: Research Activities

Research Activities

1. * **Provide a detailed description of all research activities (including screening and follow-up procedures) that will be performed for the purpose of this research study. This description of activities should be complete and of sufficient detail to permit an assessment of associated risks.**
There will be a total of 7 study visits (not including physical therapy sessions). The duration of this visit will be approximately 3.5-4 hours. The events of each visit are as follows

Screening Visit: All the following screening procedures are being completed for the purpose of this research study.

1.) Obtain Informed Consent, assignment of subject unique identifier

2.) Medical record chart review: The investigator and or study staff will perform a medical chart review (pertaining to the trauma event and surrounding surgical and medical procedures) if such records are available and presented to the investigators.

If the subject has been followed at UPMC facilities, the investigator and / or study staff will perform a medical history review (pertaining to the trauma event and surrounding surgical and medical procedures). This review will consist of prior procedures to include, but not be limited to blood tests (including but not limited to complete blood count (CBC) with Differential and Platelets, comprehensive chemistry panel, urinalysis, and culture results) operative procedures, physical therapy assessments, consultations, CT/ MRI scans, EKG, Chest X-rays, history and physical exams and any culture results, operative notes and EMG / functional tests with evaluations, history and physical exams of the affected area including notations on the extremity to be operated upon, and any other information that could directly affect the outcome of the proposed surgical procedure.

If medical records do not accompany the subject or are not available at the time of screening evaluation for investigator review, the investigator in lieu of direct medical record review will accept direct report from the referring physician, physical therapy or other referral source and /or subject self-report. This history information will be documented to the subject research chart and will consist of past medical /surgical history pertaining to the affected area of extremity injury and/or events surrounding the extremity trauma.

It may be possible that potential subject's medical records are not available/accessible at time of subject's screening and eligibility determination. Should this be the situation the investigator, MD will make eligibility determination through a thorough review of a collection of findings related to but not limited to physical examination, screening lab values, referral physician direct report, physical therapy or other referral direct reports and /or subject self-report, study physical therapy evaluations all pertaining to past extremity injury and current status of the

affected area of interest. The Investigator will base determination of subject study eligibility on the combination of the above research screening evaluation criteria.

3.) Performance of a history and physical exam completed by the investigator will include collection of participant's height and weight for calculation of BMI (https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi-m.htm).

4.) Collection of subject's medication profile, collection of subject's vital signs (Temperature, Respirations, Heart Rate, and Blood Pressure), surgical history, and collection of allergies will be conducted.

5.) Demographic information collection which may include relationship status, highest level of education completed, employment status, etc., and may be received by subject direct report.

6.) All female participants who are of child bearing potential will receive a urine pregnancy dip test.

7.) CT (completed as primary test, dependent on if the affected extremity has metal / shrapnel fragments intact) or MRI scan with 3D Rendering without contrast dye will be obtained to the area of interest. This scan will be in conjunction with morphometric measurements to accurately define the limits and extent of muscle tissue deficit.

8.) Physical therapy evaluation of affected and contralateral extremity will be performed. This evaluation will include a comprehensive functional analysis (strength and range of motion) of the affected extremity, as well as an evaluation of the contralateral extremity (if possible), for comparison.

9.) Electromyography (EMG)/Nerve Conduction Velocities (NCVs) will be performed to the area of interest to assist with evaluation and determination of functional deficit as a muscle mass defect must be associated with a functional deficit for the patient to be eligible for inclusion in this study.

10.) Collection of blood work (Serum Albumin and Pre albumin for assessment of participant's nutritional status and a CBC with Differential and Platelet count, Liver function Panel to include (Bilirubin, AST, ALT, ALP, albumin and PTT), PT/INR, and Comprehensive Chemistry panel to screen for active disease). A total of approximately 15cc of blood will be collected from the subject for this test time point and processed to evaluate subject safety prior to eligibility determination.

If abnormal blood results (i.e., CBC, LFTS, etc.,) are encountered, subject eligibility will be held and a patient referral to their PCP will be provided for evaluation. Given that elevations may arise and be transient due to other medications (i.e., CBC, LFT, etc.,), these subjects may be reconsidered after PCP evaluation and repeat labs demonstrate stability with normal values.

Upon completion of all screening procedures the investigator will evaluate all screening procedure results and based upon the study inclusion and exclusion

criteria make a determination of subject eligibility for study participation. After all screening procedures have been completed and reviewed by investigators, the subject may need to return to the Aesthetic Plastic Surgery Center for a brief follow up/exam or review of screening information. Once the PI has determined that the subject has met the eligibility criteria to participate in the study, the subject will begin their 16 week pre-operative physical therapy training sessions.

Pre-operative standard of care physical therapy training sessions: Duration will be up to 16 weeks, with frequency to be determined and monitored by the physical therapy professional. Individualized (based on the affected area) preoperative protocol of physical therapy that will optimize the strength and motion of the treated limb, as well as treat the contralateral limb (and consider reimbursement), as necessary. Each subject will have a physical therapy regimen appropriate for their injury, designed in consultation with the Physical Medicine and Rehabilitation Service. The study surgical procedure will occur once the subject has "plateaued" in performance, defined as the point when the patient fails to improve in strength and functional testing over the course of two weeks, as determined by the treating physical therapist. Such a decision would be similar clinical judgment standards used to determine when a Medicare patient is no longer making sufficient functional improvements to justify ongoing treatment. Subjects who fail to reach a plateau within the 16-week timeframe will not advance to the operative procedure and will be withdrawn from study participation.

NOTE: The external site standard of care pre-op physical therapy may be completed through telemedicine. This would be determined on a case by case basis, but would allow a participant who has already begun physical therapy, who lives in an area that is under increased restriction or shelter in place order, to continue their physical therapy.

Preoperative Visit 1: The subject will return to UPMCs Aesthetic Plastic Surgery Center prior to the surgical procedure for completion of the following research procedures. The total duration of this visit is approx. 1.5-2 hours: The procedures may occur over multiple dates, but all must be completed within 30 days of the surgical procedure.

1.) Performance of a limited/brief medical history review and physical exam inclusive of extremity area of interest to be completed by Investigator (OR by the Pre-op center as part of pre-op testing and labs, see 3 and 5 below).

2.) All female participants who are of childbearing potential will receive a urine pregnancy dip test. If the test result is positive the subject will not continue participation in this research study.

3.)Chest X-ray AP and Lateral to be completed if deemed medically necessary by study physicians.

4.) Collection of subject's medication profile, vital signs, allergies, and weight to calculate BMI measurement
(https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi-m.htm)

5.) Pre-Operative Laboratory tests will be obtained via a peripheral stick performed by laboratory personnel located on the 5th floor of the UPMC MUH building or on the 1st floor of UPMC Magee to include Serum CBC with differential, comprehensive chemistry panel (to include liver function tests and serum albumin), pre-albumin and PT/ PTT/ INR and collection of a routine urinalysis. A total of approximately 15cc of blood will be collected from the subject for this time point and processed to evaluate subject safety prior to the operative procedure.

6.) Electrocardiogram (EKG) to be completed if deemed medically necessary by study physicians.

7.) Physical therapy evaluation of affected and contralateral extremity will be performed. This evaluation will include a comprehensive functional analysis (strength and range of motion) of the affected extremity, as well as an evaluation of the contralateral extremity (if possible), for comparison.

8.) Adverse event collection

9.) The subject will be given a pain log with instructions to begin collection during post-operative Physical Therapy (even if still hospitalized) and to continue through post-operative visit 3 (month 1). The subject will record level and type of pain, interventions and outcomes for each episode of pain. The subject will be instructed to bring all forms to the post-operative office visits beginning at postoperative visit 1 (3-6 days) for collection and receipt of new forms.

Operative Visit: Performance of the surgical intervention will occur within 30 days of preoperative visit 1: The device used in this protocol has 510K clearance from the FDA for the purpose of this research study.

This operative procedure will be conducted at Magee Womens or Shadyside Hospital surgical suites. Medical record review will be completed prior to the operation. The time to complete this surgical procedure will be approximately 3-3.5 hours.

XENMATRIX™ AB, an ECM material that functions outside of the body's cells to lay a framework to provide structural support for cells to grow on, will serve as the created physiological environment for the cells to interact within the host tissue. This implant device will provide a resorbable scaffold that is replaced by the subject's own soft tissue. Consistent with the device labeling intended use for implantation to reinforce soft tissue where weakness exists and for surgical repair of damaged or ruptured soft tissue, this procedure will be performed when there are tendon units available that can be approximated. Reinforcement with the XENMATRIX™ AB implant should help to restore integrity. Based on patterns of military trauma, we expect to treat defects that include injury to the quadriceps region and biceps region.

The operative and anesthesia procedures will follow the same clinical standard as all operative procedures. Subjects will be maintained NPO in accordance with standard anesthesiology procedure. We are not deviating from the operative

standard for this application pertaining to the sterile prep, operative accessing and removal of scar tissue, repair of tendon and placement of the XENMATRIX™ AB, implant material for the affected extremity.

With this surgical procedure, the subject will be given general anesthesia during the entire procedure and after induction of anesthesia standard sterile skin preparation and draping procedures will be employed along with appropriate use of intravenous antibiotics will be implemented. The surgeon will apply tourniquet control dependent upon the anatomic location. For injuries of the upper or lower extremities, an incision will be made at the site of injury and the soft tissues dissected to expose the damaged edges of muscle and tendon. Scar tissue will be sharply debrided from the wound with great caution taken to preserve neurovascular structures. It is anticipated that these tendon units will be frayed and weakened and this (tenolysis) procedure will separate existing tendons in the damaged tissue from scar tissue and allow for movement of the tendon. Disrupted tendon bands and musculotendinous units (exact findings will vary between patients) will be repaired directly with permanent sutures in preparation of the placement of XENMATRIX™ AB extracellular matrix. The tension of the tendon repair will be set based on surgical judgment and the ECM will be prepped and implanted per manufacturer IFU instruction. After obtaining adequate hemostasis, the wound will be closed in a layered fashion. Surgical drains will be used if needed, with a determination made at the time of surgery by the attending surgeon. This type of construct is identical to that used in pre-clinical animal studies and a prior pilot study, IRB PRO#18070586.

Prior to the XENMATRIX™ AB, material placement and while the surgical muscle tissue bed is exposed a small core needle biopsy of the operative extremity area will be performed. Using a standard small core biopsy needle, the surgeon will collect approximately 1 -5 grams of tissue sample. These samples will be transported per the United States Department of Transportation (US DOT) 49 CFR Code of Federal Regulations to the laboratory area in McGowan Institute for Regenerative Medicine and place under the controls /supervision of Stephen Badylak, DVM, Ph.D., MD. A chain of custody form will be used to document specimen collection, transportation, and receipt at the lab (the subject's ID code will be recorded on this form and specimen). The de-identified samples will undergo histological processing upon arrival to the lab. will then be implanted to reinforce the tendon repair and sutured in place.

The subject will be taken to the recovery room where he/she will remain for approximately 2-3 hours to then be admitted to inpatient recovery for approximately 48-72 hours observation and immediate post-surgical assessment/care.

The physical therapy evaluator will begin gentle active range of motion exercise within 24-72 hours of surgery to maintain tendon excursion. Individualized (based on the affected area) postoperative protocol of physical therapy will vary based on the specific case. The postoperative protocol will include instruction of exercise for the subject to perform in his/her home environment. These physical therapy evaluations will begin while the subject is inpatient, prior to the subject's discharge from the hospital and may occur over multiple dates.

The surgeon PI and/or co-investigator who is a physician will determine when the subject is stable to be discharged from the hospital. At the time of discharge, the subject will be given standard postoperative instruction for the immediate care and management of the affected area. The MD will evaluate the subject's physical status, once the subject is deemed clinically stable; the physician will order local physical therapy to commence with the subject's physical therapy training sessions beginning upon hospital discharge.

Postoperative standard of care physical therapy training sessions at the subject's local facility (duration up to 6 months, with frequency to be determined and monitored by the physical therapy professional).

NOTE: The external site standard of care post-op physical therapy may be completed through telemedicine. This would be determined on a case by case basis, but would allow a participant who has already begun physical therapy, who lives in an area that is under increased restriction or shelter in place order, to continue their physical therapy.

Each study follow-up visit may occur over multiple dates, but all procedures must occur within each visit's specified window duration.

Post Operative Visit 1 (3-6 days) Safety visit: The subject will return to UPMCs Aesthetic Plastic Surgery Center after the surgical procedure for completion of the following research procedures. The total duration of this visit is approx. 0.5-1.5 hours:

1.) Performance of a limited history and physical exam, medical record review completed by Investigator.
2.) Collection and review of pain log (1-10 analog scale) place to research chart and distribute new pain logs.
3.) Collection of subject's medication profile, allergies, and vital signs
4.) Adverse Event Collection

Post Operative Visit 2 (7-14 days +/- 2 days): The subject will return to UPMCs Aesthetic Plastic Surgery Center after the surgical procedure for completion of the following research procedures. During the 7-14 day postoperative period, the study visit may occur over 2 days due to clinical safety (i.e. assessment of incision site, suture removal, drain pull, etc.), or occur on the same day as the safety visit. The total duration of this visit is approx. 1.5-2 hours:

1.) Performance of a limited history and physical exam, medical record review completed by Investigator.
2.) Collection of medication profile, vital signs, allergies, weight for BMI (https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi-m.htm)
3.) Collection and review of pain log (1-10 analog scale) place to research chart and distribute new pain logs.
4.) Physical therapy evaluation of affected and contralateral extremity will be performed. This evaluation will include a comprehensive functional analysis (strength and range of motion) of the affected extremity, as well as an evaluation of

the contralateral extremity (if possible), for comparison.
5.) Adverse event collection

Post Operative Visit 3 (30 days +/- 7 days): The subject will return to UPMCs Aesthetic Plastic Surgery Center after the surgical procedure for completion of the following research procedures. The total duration of this visit is approximately 2-2.5 hours.

1.) Performance of a limited history and physical exam, medical record review completed by Investigator.
2.) Collection of subject's medication profile, vital signs, allergies, and weight for BMI (https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi-m.htm)
3.) Collection and review of pain log. Pain log collection completed as of visit 3. Should issues persist related to surgical pain, the coordinator will record the events to the A/E log monitoring for resolution.
4.) Adverse event collection
5.) Physical therapy evaluation of affected and contralateral extremity will be performed. This evaluation will include a comprehensive functional analysis (strength and range of motion) of the affected extremity, as well as an evaluation of the contralateral extremity (if possible), for comparison.
6.) A small core needle biopsy of the operative extremity area will be performed at postoperative visit 3. This procedure will take place in the radiology department of Magee Womens Hospital or Presbyterian/Montefiore under ultrasound guidance. Utilizing sterile technique the site will be prepped and draped and approximately 5cc of lidocaine 1% solution will be instilled as a local anesthesia to the postoperative area. Using a standard small core biopsy needle, guided by ultrasound, the Investigator, who is a physician will collect approximately 1 -5 grams of tissue sample. These samples will be transported per the United States Department of Transportation (US DOT) 49 CFR Code of Federal Regulations to the laboratory area in McGowan Institute for Regenerative Medicine under the supervision of Stephen Badylak, DVM, Ph.D., MD. A chain of custody form will be used to document specimen collection, transportation, and receipt at the lab (the subject's ID code will be recorded on this form and specimen). The de-identified samples will undergo histological processing upon arrival to the lab.

The coordinator will call the subject within 72 hours after the biopsy procedure to obtain a subject self-report assessment of signs and symptoms of an adverse event post-biopsy (bleeding or signs or symptoms of infection) as standard of care follow-up to a procedure. If the subject has any issues or concerns, the study physician will evaluate the appropriate clinical intervention to be administered and based on the treating physician's discretion, this study related intervention could consist of antibiotic treatment, physical evaluation of the subject, up to and including hospitalization.

Post Operative Visit 4 (8-10 weeks +/- 2 weeks): The subject will return to UPMCs Aesthetic Plastic Surgery Center post the surgical procedure for completion of the following research procedures. The total duration of this visit is approx. 1.5-2 hours:

1.) Performance of a limited history and physical exam, medical record review

completed by Investigator.
2.) Collection of subject's medication profile, vital signs, allergies, and weight to calculate BMI measurement (https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi-m.htm)
3.) Adverse event collection
4.) Physical therapy evaluation of affected and contralateral extremity will be performed. This evaluation will include a comprehensive functional analysis (strength and range of motion) of the affected extremity, as well as an evaluation of the contralateral extremity (if possible), for comparison.

Post Operative Visit 5 (24-28 weeks +/- 2 weeks):
The subject will return to UPMCs Aesthetic Plastic Surgery Center post the surgical procedure for completion of the following research procedures. The total duration of this visit is approximately 3-3.5 hours:

1.) Performance of a limited history and physical exam, medical record review completed by Investigator.
2.) Collection of subject's medication profile, allergies, and vital signs inclusive of participant's weight to calculate BMI measurement (https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi-m.htm)
4.) Adverse event collection
5.) Physical therapy evaluation of affected and contralateral extremity will be performed. This evaluation will include a comprehensive functional analysis (strength and range of motion) of the affected extremity, as well as an evaluation of the contralateral extremity (if possible), for comparison.
6.) A small core needle biopsy of the operative extremity area will be performed at postoperative visit 5. This procedure will take place in the radiology department of Magee Womens Hospital or Presbyterian/Montefiore under ultrasound guidance. Utilizing sterile technique the site will be prepped and draped and approximately 5cc of lidocaine 1% solution will be instilled as a local anesthesia to the postoperative area. Using a standard small core biopsy needle, guided by ultrasound, the Investigator, who is a physician will collect approximately 1 -5 grams of tissue sample. These samples will be transported per the United States Department of Transportation (US DOT) 49 CFR Code of Federal Regulations to the laboratory area in McGowan Institute for Regenerative Medicine under the supervision of Stephen Badylak, DVM, Ph.D., MD. A chain of custody form will be used to document specimen collection, transportation, and receipt at the lab (the subject's ID code will be recorded on this form and specimen). The de-identified samples will undergo histological processing upon arrival to the lab.
7.) CT or MRI scan with 3D Rendering (dependent on if the affected extremity has metal / shrapnel fragments intact) without contrast dye will be obtained to the area of interest. This scan will be in conjunction with morphometric measurements to accurately define the limits and extent of muscle tissue deficit.
8.) Electromyography (EMG)/Nerve Conduction Velocities (NCVs)
9.) All female participants who are of childbearing potential will receive a urine pregnancy dip test. If the test result is positive the subject will not continue participation in this research study.

The coordinator will call the subject within 72 hours after the biopsy procedure to

obtain a subject self-report assessment of signs and symptoms of an adverse event post-biopsy (bleeding or signs or symptoms of infection) as standard of care follow-up to a procedure. If the subject has any issues or concerns, the study physician will evaluate the appropriate clinical intervention to be administered and based on the treating physician's discretion, this study related intervention could consist of antibiotic treatment, physical evaluation of the subject, up to and including hospitalization.

All research procedures will be performed at the UPMC Aesthetic Plastic Surgery Center in a private room with the exception of the chest X-rays, CT/ MRI scans, EMG, Physical Therapy function evaluation, Ultrasound guided biopsy sampling and laboratory tests which will take place at Magee Womens, Presbyterian or Montefiore Hospitals. Physical Therapy function evaluation will occur at the UPMC Centers for Rehab services. Physical Therapy Training sessions will occur at the subject's local facility.

Digital Recordings: All digital records (i.e. photography or video) obtained during any or all of the subject's pre-operative, operative, and post-operative period, may include, but not be limited to videos of personal interviews, functional assessment testing and clinical exams or photos of follow up, biopsies, etc. will be de-identified and stored indefinitely in a secure, password protected location on the UPMC server. While most recording will be de-identified, some may retain identifiers, e.g. interviews. The digital recordings are being collected for the purpose of medical education and training, publication, and media reports – and, in any mode of transmission, including and not limited to: print, email, television, internet, etc.

All participants will have a pre-op COVID test per standard of care. If a participant reported Covid symptoms to us prior to traveling, we would cancel and reschedule their research visit. If not possible due to the visit window, we would attempt to collect a partial visit through a telemedicine/remote visit or by requesting an exception to the visit window.
If a participant reported Covid symptoms after arriving in Pittsburgh, during a research visit, the participant would be treated clinically within the UPMC system (and charges may incur to the participants' insurance/self pay in this case). Research activities would be rescheduled, once the participants' treatment has been completed. Participants are made aware of this possibility, prior to their travel to Pittsburgh.

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

	Document	Category	Date Modified	Document History
View	Disabilities of the Arm, Shoulder and Hand assessment form(2)	Data Collection	9/21/2020	History
View	Patient-rated Elbow Evaluation(2)	Data Collection	9/21/2020	History

	Document	Category	Date Modified	Document History
View	Foot and Ankle Ability Measure(2)	Data Collection	9/21/2020	History
View	Hip Outcome Score(2)	Data Collection	9/21/2020	History
View	Knee Outcome Survey(2)	Data Collection	9/21/2020	History
View	Lower Extremity Function Scale(2)	Data Collection	9/21/2020	History
View	Neck Disability Index(2)	Data Collection	9/21/2020	History
View	Oswestry Low Back Pain Disability Questionnaire(2)	Data Collection	9/21/2020	History
View	Patient Rated Wrist Evaluation(2)	Data Collection	9/21/2020	History
View	PAIN LOG Instructions5.21.2019.doc(0.01)	Data Collection	5/21/2019	History
View	Subject pain log(0.01)	Data Collection	5/21/2019	History

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

● **Yes** ○ No

*** Provide the volume per withdrawal, total volume and frequency, and qualifications of individual performing the procedure:**
Screening: Serum albumin and pre-albumin for assessment of participant's nutritional status and a CBC with differential and platelet count, PT/PTT/INR, and comprehensive chemistry panel to screen for active disease and review liver function (approximately 15 cc total).

Pre-Op: Serum CBC with differential, comprehensive chemistry panel, serum albumin, pre-albumin and PT/ PTT/ INR and collection of a routine urinalysis. A total of approximately 15cc of blood will be collected from the subject for both of these test time points and processed to evaluate subject safety

Consent Process

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

1. * **Indicate where the consent process will take place and at what point consent will be obtained:**
Once subjects have been determined to be eligible after the telephone screening, he or she will come to the Department of Plastic Surgery Aesthetic Center where the consent process will take place in a private room, prior to beginning any research study procedures.

2. * **Describe the steps that will be taken to minimize coercion and undue influence, including assurance that there is sufficient time for subjects to make an informed decision:**
The study investigator or co-investigator along with the research coordinator will discuss with the subject the nature of the research study, design schema, the risks and benefits, cost and payments and rights as a research subject participant. The potential subject will review the informed consent document allowing ample time to review all information and ask questions. Should the potential subject wish to take the consent and review it outside of the office setting or discuss with other family, medical personnel he/she will be able to leave the office and return at a later date. The study investigator will provide the potential subject a private area to conduct this informed consent document review prior to signing the informed consent.

3. **For studies that involve multiple visits, describe the process to ensure ongoing consent:**
Ongoing assessment of voluntary consent desired by the subject will be conducted verbally at each visit, reminding subjects that their continued participation is voluntary and may be terminated at any point. The subject's continued consent for study participation will be documented contemporaneously. This process will be documented in the coordinator's visit note. Subjects will be updated about study modifications, as applicable while they are participants and re-consent forms will be obtained from the subject, as applicable.

4. * **Steps to be taken to ensure the subjects' understanding:**
The Investigator will discuss with the subject the nature of the research study, design schema, the risks and benefits, cost and payments and their rights as a research subject. The potential subject will review the informed consent document allowing ample time to review all information and ask questions. The Investigator will provide the potential subject a private area to conduct this study document review prior to signing the informed consent. After this detailed discussion of the study and conclusion of any questions, the study investigator, who is a physician, will obtain informed consent. The research coordinator will document the consenting process and prior to beginning any research activities provide a copy of the fully executed informed consent document to the subject for his or her records. If a re-consenting process is required based on regulatory guidance, the subject will be re-consented

at their next scheduled visit or at an interim visit determined to be necessary for subject safety. The research member will highlight all changes with the subject while providing opportunity for the subject to review at their leisure and make an informed decision to continue or discontinue study participation based on these changes. Technical terms will be described using lay terminology and that subjects are permitted and encouraged to ask questions, and all will be answered to their satisfaction.

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

○ Yes ◉ **No**

View: Pitt SF: Consent Forms

Consent Forms

1. **Consent Forms:**

	Document	Category	Date Modified	Document History
View	UPITT Rubin_Consent MTEC(10.01)	Consent Form	1/21/2022	History

Refer to the following templates and instructional documents:

- Guidance - Consent Wording
- Template - Consent Document - Short Form
- HRP-090 - SOP - Informed Consent Process for Research
- HRP-091 - SOP - Written Documentation of Consent

Medical Records

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

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

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

Information to be collected from the medical record are clinical details pertaining to:

Preoperative assessments by clinical staff, physiotherapy at multiple time points, laboratory result values, radiology tests and procedures such as CT/MRI scans, X-rays, ultrasound guided biopsy procedures, past medical information that directly impacts the safety determination for the subject to participate in this study.

Intraoperative data recorded by the attending surgeon, anesthesiologist and all responsible OR staff under their supervision

Postoperative information in the immediate and longer-term recovery period up to 30 weeks collected by the physical therapist, physician notes, consulted or subject MD visits and all named investigators as they pertain to any potential safety evaluations as they may relate to participation to this study.

Information derived from research procedures, examples of which include the surgical /operative reports, record of biopsy taken, lab value results, and post-operative physical assessments may be placed into the medical record, along with a copy of your consent form.

2. *** Describe what protected health information will be obtained from a non-UPMC/Pitt covered entity for research purposes and how the HIPAA requirements will be met:**

If the subject is coming from an entity outside of UPMC, he/she may bring copies of their medical records to the screening visit, or he/she may voluntarily send records in anticipation of the visit for the Investigator's screening/eligibility evaluation. We will look at all records that are provided appropriate to the study and may include the following: all information pertaining to the trauma event and surrounding surgical and medical procedures, prior procedure blood tests (including but not limited to complete blood count (CBC) with Differential and Platelets, comprehensive chemistry panel, urinalysis, and culture results) operative notes, physical therapy assessments, consultations, prosthetic/orthotics evaluation/ history, CT, MRI scans, EKG, Chest X-rays, history and physical exams, and any other information pertaining to the affected injury, limb trauma that could directly affect the outcome of

the proposed surgical procedure. Research data will not be placed in non-UPMC/Pitt medical records.

Electronic Data Management

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

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

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

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

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

c: List any other unique identifying numbers, characteristics or codes related to an individual that are to be collected: None.

d: Will you be collecting any data subject to the General Data Protection Regulation (GDPR)? ○ **Yes** ◉ **No**

* **e: Provide a justification for recording Social Security numbers including why it's required, where it's stored, how it's protected and who will have access:** For Vincent Use only. It will be stored in a locked cabinet with the original consent form. Only the study team will have access.

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

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

* **Briefly describe your plan to store coded data separately from the identifiable data:**	Identifiable data will be maintained in hard copy only (data will not be stored electronically) with the original informed consent form in a separate area than the shadow chart. All identifiable information fields in the shadow chart will be redacted to remove any ability to be linked without subject identifier.

2. * **During this study, will restricted data as defined by the University's Data Risk Classification matrix (** https://www.technology.pitt.edu/security/data-risk-classification-and-compliance **) be processed, stored, or transmitted?**
○ Yes ◉ **No**

3. * **During this study, will sensitive data** (https://www.hrpo.pitt.edu/electronic-data-security) **be collected where disclosure of identifying information could have adverse consequences for subjects or damage their financial standing, employability, insurability, educational advancement, reputation or place them at risk for criminal or civil liability?**
◉ **Yes** ○ No

4. * **Select all locations where data will be stored or accessed (including e.g.,** personal / employer laptop or desktop**): All locations where data will be processed, stored, and transmitted must be in compliance with** University of Pittsburgh Research Data Management Interim Policy RI 14.

	Storage Device	Description	Identifiable Data	Sensitive Data	De-Identified/Anonymous Data
View	Server: UPMC Managed Server	Relevant clinical data will be stored per UPMC protocols in a HIPAA-compliant manner. No other electronic or physical records will be maintained outside of UPMC secured firewalls and within approved facilities.	no	yes	yes
View	UPMC owned desktop, laptop or other device	Relevant clinical data will be stored per UPMC protocols in a HIPAA compliant manner. No other electronic or physical records will be maintained outside of UPMC secured firewalls and within approved facilities.	no	yes	yes

*** Select all technologies being used to collect data or interact with subjects: Technologies selected in this section may require a Vendor Security Risk Assessment, which can be requested here.**

Electronic audio, photographic, or video recording or conferencing

N/A

*** Video, Audio, Images – identify all uses of video, audio, photography, etc. to be used to collect data during any phase of the research:**

name	Identifiable
View Digital photography	no
View Video recording	yes

Data Safety and Monitoring

1. * **Describe your plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe. The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor:**
The Data Safety and Monitoring Plan for this research study will consist of two parts. A Local Data and Safety Monitoring Plan will be implemented by the Principal Investigator to ensure that there are no changes in the risk/benefit ratio during the course of the study and that confidentiality of research data is maintained. This local DSMB will consist of the PI, Co-Investigators and study personnel who will meet and discuss monthly the study (e.g., study goals and modifications of those goals; subject recruitment and retention; progress in data coding and analysis; documentation, identification of adverse events or research subject complaints; violations of confidentiality) and address any issues or concerns at that time. Minutes will be kept for these meetings and will be maintained in the study DSMB binder. Any instances of adverse events will be reported immediately to the University of Pittsburgh UPITT HRPO in accordance with the guidance on the UPITT HRPO website.

The annual UPITT HRPO renewal for this study will include a summary report of the Data and Safety Monitoring Plan findings from the study for the prior year. We will include the following information at the time of the UPITT HRPO renewal regarding the frequency of the monitoring, the dates that the monthly meetings took place, a summary of the cumulative adverse events, external factors or relevant information that might have an impact on the safety or ethics of the study, and final conclusions regarding changes to the anticipated risk/benefit ratio to study participation and final recommendations related to the continuation, changing, or termination of the study.

The second part of the DSMP will be the inclusion of an Medical Monitor. Dr. Joseph Losee, MD (Chief, Pediatric Plastic Surgery and Program Director, Plastic Surgery Residency and Ross H. Musgrave Endowed Chair, Pediatric Plastic Surgery) who will act as the Medical Monitor for this study and will meet once a year or Ad Hoc for review of all unanticipated events, adverse events, and serious adverse events affecting the risk to the human subject or others. Without any involvement in this research protocol, he is not under the supervision of the PI nor does he hold a conflict of interest related to this project. Dr. Losee is available on site to respond to any urgent or emergency situations that may arise during the study and to serve as the subject advocate. The Medical Monitor is required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, he as a Medical Monitor must comment on the outcomes of the event or problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. He will also indicate whether he concurs with the details of the report provided by the principal investigator. As the Medical Monitor he has the authority to stop the research at any time; he can remove individuals from the study, and take any steps necessary to protect the safety and

well being of participants until the UPITT HRPO has time to assess the study. He may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research; He shall have the responsibility to promptly report their observations and findings to the USAMRDC ORP HRPO. Dr. Losee will evaluate any adverse events and research staff adherence to subject confidentiality and de-identification processes. He will discuss, ad hoc, any changes to the risk/benefit ratio of this study for the PI's report to the local UPITT HRPO of all reporting adverse events, external factors or relevant information that might have an impact on the safety or ethics of the study, and final conclusions regarding changes to the anticipated risk/benefit ratio to study participation and final recommendations related to the continuation, changing, or termination of the study as outlined by the University of Pittsburgh HRPO.

The protocol will be not be initiated until written notification of approval of the research project is issued by the UPITT HRPO. A copy of the approved continuing review report and the local UPITT HRPO approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available. A copy of the approved final study report and local UPITTHRPO approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available. Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the UPITT HRPO for approval prior to implementation. The USAMRMC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review), or a change that could potentially increase risks to subjects. All other amendments must be submitted with the continuing review report. All unanticipated problems involving risk to subjects or others must be promptly reported by phone (301-619-2165), by email (HRPO@amedd.army.mil), or by facsimile (301-619-7803) to the HRPO. A complete written report will follow the initial notification. In addition to the methods above, the complete report can be sent to the US Army Medical Research and Materiel Command, ATTN: MCMR-RP, 504 Scott Street Fort Detrick, Maryland 21702-5012 Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the UPITT HRPO, the institution, the sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.A copy of the continuing review report and the re-approval notification by the UPITT HRPO must be submitted to the UPITT HRPO as soon as possible after receipt of approval. Please note that the HRPO also conducts random audits at the time of continuing review and additional information and documentation may be requested at that time. The final study report submitted to the UPITT HRPO, including a copy of any acknowledgement documentation and any supporting documents must be submitted to the UPITT HRPO as soon as all documents become available. The knowledge of any pending compliance inspection/visit by the Food and Drug Administration (FDA), Office for Human Research Protections, or other government agency concerning this research; the issuance of inspection reports, FDA Form 483, warning letters, or actions taken by any regulatory agencies including legal or medical actions; and any instances of serious or continuing noncompliance with the regulations or requirements must be reported immediately

to the UPITT HRPO. Accurate and complete study records will be maintained and made available to representatives of the USAMRMC as a part of their responsibility to protect human subjects in research. All research records are stored in a confidential manner so as to protect the confidentiality of subject information. Per DoD Directive 3216.02, all greater than minimal risk studies require a Medical Monitor. The USAMRMC ORP HRPO also reserves the authority to require assignment of a Medical Monitor for those protocols assessed as presenting no greater than minimal risk to the subjects participating in the study.

2. * **Describe your plan for sharing data and/or specimens:**
Data and samples resulting from this research study may be shared with other investigators in the future, and all information will be de-identified prior to the sharing of this information.

3. **If any research data is collected, stored, or shared in a paper format, address what precautions will be used to maintain the confidentiality of the data:**
Any information about the subject obtained from or for this research study will be kept as confidential (private) as possible. All records related to the subject's involvement in this research study will be kept in a locked file cabinet or in a password protected computer database accessible only to study personnel as described above. The identity on these records will be indicated by a unique study number, rather than by name, and the information linking this study number with the subject's identity will be kept separate from the research records. The subject will not be identified in any publication of the research study.The digital recordings are being collected for the purpose of medical education and training, publication, and media reports – and, in any mode of transmission, including and not limited to: print, email, television, internet, etc. All digital records (i.e. photography or video) obtained during any or all of the subject's pre-operative, operative, and post-operative period, may include, but not be limited to videos of personal interviews, functional assessment testing and clinical exams or photos of follow up, biopsies, etc. will be de-identified and stored indefinitely in a secure password protected, location on the UPMC server.

Specimens and Related Data

1. * **Data and Specimens will be stored:**
   Limited time (i.e., only until the study is completed)

2. * **Indicate the type of specimen, describe where stored, and for how long:**
   A small core needle biopsy of operative extremity area will be performed using a standard small core biopsy needle, guided by ultrasound, the Investigator, who is a physician will collect approximately 1-5 grams of tissue sample. These samples will be transported per the United States Department of Transportation (US DOT) 49 CFR code of Federal Regulations to the laboratory area in McGowan Institute for Regenerative Medicine under the supervision of Stephen Badylak, DVM, PhD, MD.These specimens will be stored for the duration of the study.

3. * **How the specimens will be accessed and who will have access to the specimens:**
   The PI (Rubin), Dr. Badylak and appropriate team members under the PI's oversight will have access to the biopsy specimens and only with permission will the samples be accessed.The de-identified samples will undergo histological processing upon arrival to the lab and the handling, processing, storage and recording of these samples will occur by properly trained team members under the supervision of Dr. Badylak and the study PI. These specimens will be stored for the duration of the study.

4. * **List the data to be stored or associated with each specimen:**
   A chain of custody form will be used to document specimen collection, transportation and receipt at the lab (the subject's ID code will be recorded on this form and specimen). The de-identified samples will be stored with a linkage code to the protocol.

5. * **Describe the procedures to release data or specimens, including the process to request a release, who can obtain data or specimens, the data to be provided with the specimens:**
   Dr. Badylak will control access to samples and the oversee sharing. None is currently planned but Drs. Rubin and Badylak will authorize any future sharing, to include an approved data use or materials transfer agreement.

Risk and Benefits

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

View

Research Activity	**Risks of the MRI:**
Common Risks	**Experimental Interventions: potential ear discomfort from loud noise and claustrophobia or fear of confined spaces, excessive anxiety. Follow up Procedures: potential ear discomfort from loud noise and claustrophobia or fear of confined spaces, excessive anxiety.**
Infrequent Risks	***No Value Entered***
Other Risks	**Experimental Interventions: There is a potential risk of the strong magnetic field of the scanner attracting metallic objects toward the magnet. There are certain conditions that would exclude the subject from having a MR study. Follow up Procedures: There is a potential risk of the strong magnetic field of the scanner attracting metallic objects toward the magnet. There are certain conditions that would exclude the subject from having a MR study. These conditions include the presence or suspected presence of a heart pacemaker, aneurysm clip, ear implant, IUD, shrapnel or metallic fragments in or on the body or eyes, neuro-stimulators, or other metal devices. No other serious effects have been reported from being in the 1.5 Tesla magnet, although vertigo (e.g., dizziness and nausea) has been reported at higher field strengths. To minimize these risks, the subject will be carefully screened for metallic objects in their possession before entering the magnet room.**

View

Research Activity	**Risks from reactions to anesthetic medicines**
Common Risks	***No Value Entered***
Infrequent Risks	***No Value Entered***
Other Risks	**Experimental Interventions: Some anesthetic medicines may cause allergic or other abnormal reactions in some people, but these are rare. If you suspect you may have such a problem, you should tell both your surgeon and anesthesia specialist well before your surgery. Testing will then be arranged as necessary. A rare, potentially fatal condition called malignant hyperthermia (MH) may be triggered by some anesthetics. The anesthetics most commonly associated with malignant hyperthermia include the inhalation anesthetics and the muscle relaxant medicines.**

View

Research Activity	**Risk of Venipuncture (blood draw)**
Common Risks	***No Value Entered***
Infrequent Risks	**Screening Procedures: Infrequent (Occurs in 1% to 10% or 1 to 10 out of 100 people): mild pain and discomfort at the injection or needle insertion site as well as possible infection, bleeding, bruising and soreness. Experimental Interventions: Infrequent (Occurs in 1% to 10% or 1 to 10 out of 100 people): mild pain and discomfort at the injection or needle insertion site as well as possible infection, bleeding, bruising and soreness.**
Other Risks	**Screening Procedures: Rare (Occurs in less than 1% or less than 1 out of 100 people): severe pain; swelling; possibly an infection from the actual injection; fainting. Experimental Interventions: Rare (Occurs in less than 1% or less than 1 out of 100 people): severe pain; swelling; possibly an infection from the actual injection; fainting.**

View

Research Activity	**Physical therapy evaluations**
Common Risks	***No Value Entered***
Infrequent Risks	***No Value Entered***
Other Risks	**During strengthening and stretching protocols, there is a risk that the patient may experience muscle discomfort/ pain, muscle strain, or fatigue. These risks will be minimized by providing detailed explanations and demonstrations of all exercises and interventions prior to any participant activity, allowing all activities to be voluntary and able to be stopped at any time, including optional rest periods, initial supervision and spotting of all participants. Spotting will be performed by trained therapists. In the case of a fall, participants will be immediately evaluated by a therapist who has been trained in determining the level of severity of potential injury, and in the event of injury, one of the physician investigators associated with this study will be notified immediately by telephone so the situation can be described and his/ her recommendation for further care can be followed. Any emergency medical care, if needed, will be sought at the local hospital. Subjects will be informed that they will need to communicate any discomfort that they experience during physical therapy evaluation session**

View

Research Activity	**Risks of Electromyography (EMG):**
Common Risks	**Experimental Interventions: People usually have a small amount of discomfort during EMG testing because of pin insertion. Disposable needles are used so there is no risk of infection. During nerve conduction studies, small electrodes are taped to the skin. Follow up Procedures: People usually have a small amount of discomfort during EMG testing because of pin insertion. Disposable needles are used so there is no risk of infection. During nerve conduction studies, small electrodes are taped to the skin or placed around fingers. The subject typically experience a brief and mild shock, which may be a bit unpleasant. Most people find it only slightly annoying.**
Infrequent Risks	***No Value Entered***
Other Risks	***No Value Entered***

View

Research Activity	**Surgical Anesthesia**
Common Risks	**Although all types of anesthesia involve some risk, major side effects and complications from anesthesia are uncommon. Your specific risks depend on your health, the type of anesthesia used, and your response to anesthesia. Some people who are going to have general anesthesia express concern that they will not be completely unconscious but will "wake up" and have some**

		awareness during the surgical procedure. Awareness during general anesthesia is very rare because anesthesia specialists devote careful attention and use many methods to prevent this.
	Infrequent Risks	General anesthesia suppresses the normal throat reflexes that prevent aspiration, such as swallowing, coughing, or gagging. To help prevent aspiration, an endotracheal (ET) tube may be inserted during general anesthesia. When an ET tube is in place, the lungs are protected so stomach contents cannot enter the lungs. Aspiration during anesthesia and surgery is very uncommon. To reduce this risk, people are usually instructed not to eat or drink anything for a specific number of hours before anesthesia so that the stomach is empty. Anesthesia specialists use many safety measures to minimize the risk of aspiration. Insertion or removal of airways may cause respiratory problems such as coughing; gagging; or muscle spasms in the voice box, or larynx (laryngospasm), or in the bronchial tubes in the lungs (bronchospasm). Insertion of airways also may cause an increase in blood pressure
	Other Risks	These include changes in blood pressure or heart rate or rhythm, heart attack, or stroke. Death or serious illness or injury due solely to anesthesia is rare and is usually also related to complications from the surgery. Death occurs in about 1 in 250,000 people receiving general anesthesia, although risks are greater for those people with serious medical conditions. Serious side effects of general anesthesia are uncommon in people who are otherwise healthy. But because general anesthesia affects the whole body, it is more likely to cause side effects than local or regional anesthesia. Most side effects of general anesthesia are minor and can be easily managed.
View	Research Activity	Risk of Chest X-ray
	Common Risks	Experimental Interventions: The chest x-ray is one of the lowest radiation exposure medical examinations performed today. The effective radiation dose from this procedure is about 0.1 mSv, which is about the same as the average person receives from background radiation in 10 days.
	Infrequent Risks	*No Value Entered*
	Other Risks	*No Value Entered*
View	Research Activity	CT Scan-Risks of Radiation Exposure
	Common Risks	Study Procedures: This study will involve exposure to radiation. The amount of radiation exposure that each patient will receive will be about 1.3 rem per scan (a total of 5.2 rem) with minimum exposure of other areas of the body. There is no minimum amount of radiation exposure that is recognized as being totally free of the risk of causing genetic mutations or cancer. However, the risk associated with the amount of radiation exposure is felt to be low and comparable to everyday risks. All female study participants will be tested for pregnancy using a dip stick test to verify they are not pregnant prior to all CT scans being obtained and results will be recorded to the research chart.
	Infrequent Risks	*No Value Entered*
	Other Risks	*No Value Entered*
View	Research Activity	Ultrasound guided biopsy
	Common Risks	Bleeding: It is possible, though unusual to experience a bleeding episode during or after this procedure. Bruising may result after the biopsy due to capillary interruption, Redness, swelling, pain may result from the biopsy site post procedure

Infrequent Risks	In rare cases: Infection is unusual after this biopsy procedure, should infection occur additional treatment including antibiotics or surgery may result. Scar: the skin when healing occurs at the biopsy area may result in scar In rare cases: Infection is unusual after this biopsy procedure, should infection occur additional treatment including antibiotics or surgery may result. Scar: the skin when healing occurs at the biopsy area may result in scarring.
Other Risks	hematoma, nerve injury, infection at biopsy site. Risk of nerve or vessel damage, due to alterations in the anatomy of this type of injury.

View

Research Activity	Risk of Breach of Confidentiality
Common Risks	*No Value Entered*
Infrequent Risks	*No Value Entered*
Other Risks	Study Procedures: Participation in this research study does involve the potential risks of a breach of confidentiality of the medical record information and associated privacy of the participants. The study investigators will take steps to reduce these risks by: 1) removing direct participant identifiers (i.e., names, social security numbers, medical record numbers) from information stored in the study records; 2) securing, in a separate location, and limiting access to information linking codes assigned to the study record information with direct participant identifiers; and 3) limiting access to information contained within the study records to study investigators only.

View

Research Activity	Surgical procedure with Xenmatrix AB™
Common Risks	*No Value Entered*
Infrequent Risks	*No Value Entered*
Other Risks	Soft tissue repair is surgery, and with any surgery there may be general adverse effects or complications: • Infection after the implantation of the device could cause death or loss of limb. • The compromised skin may not heal from the surgery and amputation may be necessary. • The reconstruction may not take making the condition worse than it was before the surgery. • The muscle may be destroyed, and may never work again, regardless of the surgical outcome of the repair. • Injury to nerves and blood vessels • Fractures • Weakness • Stiffness or instability of the joint • Pain/Tenderness at the site • Scarring • Inability to repair a tendon • Re-rupture • pneumonia • cardiovascular disorders, sterile abcess and • General risks associated with surgery and anesthesia • Additional surgery as standard of care in the event of an adverse event. Additional surgery(ies) is/are considered standard of care procedures to address drain removal, hematoma development, infection, or other complications as anticipated with surgical procedures. PIs will follow protocol for the research surgery and treat complications as required by standard of care guidelines for post-operative complications. There are also a few related risks associated with the implantable device: • Stretching or tearing of the implant • Stiffness • Chronic inflammation or swelling • Longer rehabilitation period • Failure of the implant to be replaced by natural tissue • Immunological reaction • change in position or loosening of the components, • dislocation, • hematoma, • Allergic reactions or rejection of the material could occur, particularly if you have a history of multiple or severe allergies to antibiotics Rifampin and Minocycline or hypersensitivity to tetracycline or other components of the device, or have an overly sensitized immune system, or a sensitivity to pork products. Careful consideration should be used in the use of this device in with patients with compromised hepatic function.

View

Research Activity	Risks of Electrocardiogram (EKG):

Common Risks	Experimental Interventions: It is common (Occurs in 10-25% of people (10 to 25 out of 100 people) that you may experience irritation or redness at the sites where small adhesive disks are placed on the chest skin to hold the wires that are hooked to the computer that measures heart rhythm.
Infrequent Risks	*No Value Entered*
Other Risks	*No Value Entered*

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

Describe the steps that will be taken to prevent or to minimize the severity of the potential risks:

Participation in this research study does involve the potential risks of a breach of confidentiality of the medical record information and associated privacy of the participants. The study investigators will take steps to reduce these risks by: 1) removing direct participant identifiers (i.e., names, social security numbers, medical record numbers) from information stored in the study records; 2) securing, in a separate location, and limiting access to information linking codes assigned to the study record information with direct participant identifiers; and 3) limiting access to information contained within the study records to study investigators only. Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study, computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords, prior to access to any study-related information, whenever feasible, identifiers will be removed from study-related information, precautions are in place to ensure the data is secure by using password restricted and folder level access by permission only on UPMC servers. All information obtained for the purpose of this clinical trial will be de-identified and will be assigned a study ID code. All paper files will be in a locked file cabinet within the Department of Plastic Surgery offices. All computer based files are located on a secure limited-access share drive on the UPMC server.

Reference to sample: All research samples will be stored to include assigned code numbers, and any information linking these code numbers to the corresponding subjects' identities will be kept in a separate, secure location located in the security manned McGowan Institute, at the University of Pittsburgh.

Screening Procedures:Subject will be in a private room for all research procedures and during the consenting process steps will be taken to maintain to protect the potential subject's PHI. All Study materials will be assigned a study ID code. No identifiable information will be on said study materials. All information obtained for the purpose of this clinical trial will be de-identified and will be assigned a study ID code. All paper files will be in a locked file cabinet within the Department of Plastic Surgery offices. All computer based files are located on a secure limited-access share drive on the UPMC server.
All research staff are trained in research conduct and compliance having completed all required research CITI Modules and have received education in ICH GCP E6 "Good Clinical Practice" in research as well as specific protocol related research procedure education.
The UPMC Laboratory are well-versed in the risks of their practice and thoroughly

address the subject prior to each exam, inclusive of the risks of venipuncture procedure and risks of exposure to radiation. All exams will be terminated should the subject expresses any concerns issues or discomfort.
In addition to our screening and subsequent pregnancy tests, the CT technicians are well-versed in the risks and thoroughly question the subject prior to each exam, including excess exposure to radiation. All exams will be terminated as soon as the subject expresses any discomfort.

Experimental Interventions:The surgeons performing the surgical procedure with extracellular matrix device are highly trained and have extensive years of skilled training in this surgical procedure.
The anesthesiologists are highly trained and skilled with many years of clinical surgical procedures with the use of various methods of sedation.
Physical therapy evaluation sessions:In the event of injury, one of the physician investigators associated with this study will be notified immediately by telephone so the situation can be described and his/ her recommendation for further care can be followed.

Any emergency medical care, if needed, will be sought at the local hospital.
Subjects will be informed that they will need to communicate any discomfort that they experience during physical therapy evaluation session.

3. **Financial risks - will the subject or insurer be charged for any research required procedures?**
   ○ Yes ● **No**

4. **Describe the steps that will be taken to protect subjects' privacy:**
   All aspects of the study will be performed in a private room, including the consenting process, exams, urine pregnancy testing, questionnaires, photographs, CT/MRI scan, laboratory blood draw and the surgical procedure. The collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected, drapes or other barriers will be used for subjects who are required to disrobe.

5. **What steps will be taken in the event that a clinically significant, unexpected disease or condition is identified during the conduct of the study:**
   Upon discovery the PI and/or co-investigator will notify the subject of any event that could be of clinical significance needing further evaluation, or of a diagnosis of any unexpected disease or condition that occurred during the conduct of the study's research procedures. The study investigator will at the time of discovering the event contact the referring physician or primary physician for further evaluation of the event. Should the event be of critical nature needing immediate intervention, the study investigator or co-investigator will proceed with immediate clinical intervention and screening procedures will be concluded.

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

The subject may derive a direct benefit from study participation, this potential benefit being improved function and strength of the affected limb secondary to the operative procedure. Although we cannot guarantee a positive outcome from this research procedure, validating the efficacy of this treatment could provide a new approach to restore functionality, increase knowledge, and technological advancement may result from the conduct of the research study and potentially help a large number of patients in the future. A considerable amount of physiotherapy is provided to the subject so that they reach a functional plateau prior to insertion of the experimental device. Even if the experimental device is not beneficial to the subject, subjects still stand to benefit from intensive physiotherapy intervention.

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

● **Yes** ○ No

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

Development of complications (e.g., adverse reactions/events, failure to demonstrate effectiveness, disease progression and severe infection at the surgery site).

Abnormal test findings

Withdrawal of consent.

Lost to follow-up.

Severe Adverse events.

The Investigator considers that it is in the best interests of the subject not to continue.

At the request of the ethics committee or competent authority.

Noncompliance of study visits (including but not limited to completion of screening and study visit procedures).

As defined by the CTCAE v.5.0 adverse event grading scale for individual subjects below:

≥Grade 3 surgical procedure site infection

≥Grade 3 hematologic and non-hematologic toxicities

≥Grade 3 neurological toxicities

Any subject who experiences a Serious Adverse Effect related to the research procedure will receive treatment intervention and may be removed from the study, per investigator discretion. The subject will be followed by the study investigator and/or primary care physician until resolution of the event with or without sequelae.

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

Subjects will be instructed that they may choose to withdraw from this study at any time, but it is important that they continue to be monitored by a physician after they receive the research procedure in order to ensure their safety. It is also important for the subject to contact study personnel if they later experience any side effects that they might feel are related to the research study.

Should the subject decide to withdraw or be withdrawn from study participation, the already collected samples will be kept and not destroyed. It is the Principal Investigator's intention to make stored samples and subject de-identified information available to secondary investigators (investigators not listed on the front page of this consent document) after all research study testing has been completed. These stored samples and associated subject information will not include subject identifiers. The digital recordings are being collected for the purpose of medical education and training, publication, and media reports – and, in any mode of transmission, including and not limited to: print, email, television, internet, etc. All digital records (i.e. photography or video) obtained during any or all of the subject's pre-operative, operative, and post-operative period, may include, but not be limited to videos of personal interviews, functional assessment testing and clinical exams or photos of follow up, biopsies, etc. will be kept and de-identified and stored indefinitely in a secure, password protected location on the UPMC server.

Any identifiable research or medical information recorded for, or resulting from the subject's participation in this research study prior to the date that the subject formally withdraws consent will continue to be used and disclosed by the investigators for the purposes described above. All research samples will be stored to include assigned code numbers, and any information linking these code numbers to the corresponding subjects' identities will be kept in a separate, secure location located in the Department of Plastic Surgery at the University of Pittsburgh. Should the subject decide to withdraw or be withdrawn from study participation, the already collected samples and all digital recordings will be kept and not destroyed. All samples and digital recordings collected during their participation in this clinical trial, upon their early withdraw from the study, will be kept and not destroyed, but processed specifically as outlined as stated in the research design for this trial.

Upon the subject's withdrawal from the study, should they specifically request that their biological samples collected for research purposes be destroyed, we will stop all testing and destroy any remaining unprocessed samples.It is the Principal Investigator's intention to make stored samples and subject information de-identified available to secondary investigators (investigators not listed on the front page of this consent document) after all research study testing has been completed. These stored samples and associated subject information will not include subject identifiers.

View: Pitt SF: Conflict of Interest Ver2

Conflict of Interest

Institutional Financial Interests

1. * **To the best of your knowledge, has the University of Pittsburgh optioned or licensed technology that will be tested or evaluated in this research?**

○ Yes ◉ **No**

Ancillary Reviews

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

- ☐ Conflict of Interest (**COI**)
- ☐ Clinical and Translational Research Center (**CTRC**)
- ☐ Data Security
- ☐ Honest Broker
- ☐ UPMC Investigational Drug Service
- ☐ Pitt Medical School Review
- ☐ Pitt+Me
- ☐ IND & IDE Support(**IIS**)
- ☐ Radioactive Drug Research Committee (**RDRC**)(study involves the evaluation or use of procedures that emit ionizing radiation)
- ☐ ORP Business **Manager** (required for industry sponsored studies)
- ☐ Religious Directives
- ☑ Scientific Review
- ☑ Health Record Research Request (**R3**) (required if using UPMC clinical data and authorization for other UPMC data sources for research)
- ☑ UPMC Office of Sponsored Programs and Research **Support** (using UPMC facilities and/or UPMC patients during the conduct of the study)

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

- ☐ Human Stem Cell Oversight (**hSCRO**)
- ☐ Institutional Biosafety Committee (**IBC**)(study involves deliberate transfer of recombinant or synthetic nucleic acid molecules)

Good Clinical Practice (GCP) Training

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

ClinicalTrials.gov Information

Visit the University of Pittsburgh Office for ClinicalTrials.gov website or contact ctgov@pitt.edu for further information.

2. * **Was this study registered, or will it be registered, on ClinicalTrials.gov?**
   ● Yes ○ No

3. * **Is the University of Pittsburgh or UPMC the Sponsor Organization for this study record?**
   ● Yes ○ No

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

Principal Investigator of this IRB application

Supporting Documents

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

	Document	Category	Date Modified	Document History
View	FRIAR FORM(3)	Other	1/7/2022	History
View	Study Schema(4)	Other	1/7/2022	History
View	MOD 5 response to comments 1.21.20(0.03)	Other	1/22/2020	History
View	Mod 3 response to comments11.15.2019(0.01)	Other	11/15/2019	History
View	Responses to Inquiry for Clarification(0.02)	Other	8/1/2019	History
View	PBS PRICING 2(0.01)	Other	5/3/2019	History
View	PBS PRICING(0.01)	Other	5/3/2019	History
View	PSD PRICING(0.01)	Other	5/3/2019	History
View	References(1)	Other	5/1/2019	History

Add Storage Information

1. * **Select a Storage Type:**
   Server: UPMC Managed Server

2. **Description:**
   Relevant clinical data will be stored per UPMC protocols in a HIPAA-compliant manner. No other electronic or physical records will be maintained outside of UPMC secured firewalls and within approved facilities.

3. * **Will identifiable data be stored in this location?**
   ○ Yes ◉ **No**

4. * **Will sensitive data be stored in this location?**
   ◉ **Yes** ○ No

5. **Will de-identified or anonymous data be stored in this location?**
   ◉ **Yes** ○ No

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

View: Pitt Create

Add Storage Information

1. * **Select a Storage Type:**
   UPMC owned desktop, laptop or other device

2. **Description:**
   Relevant clinical data will be stored per UPMC protocols in a HIPAA compliant manner. No other electronic or physical records will be maintained outside of UPMC secured firewalls and within approved facilities.

3. * **Will identifiable data be stored in this location?**
   ○ Yes ● **No**

4. * **Will sensitive data be stored in this location?**
   ● **Yes** ○ No

   * **Define your encryption methods:**
   - **BitLocker (Windows)** (Turn on device encryption)
   - **File Vault (Mac)** (Use FileVault to encrypt the startup disk on your Mac)
   - **SecureZIP** (SecureZIP: Getting Started (Windows) | University of Pittsburgh)

   Information will be stored UPMC within secured and approved facilities

5. **Will de-identified or anonymous data be stored in this location?**
   ● **Yes** ○ No

6. * **Is anti-virus software installed and up to date on all devices and are the operating systems kept up-to-date on all devices?**
   ● **Yes** ○ No

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

View: Pitt Risk

Risk

1. * **Research Activity:**
   Risks of the MRI:

2. **Common Risks:**
   Experimental Interventions: potential ear discomfort from loud noise and claustrophobia or fear of confined spaces, excessive anxiety. Follow up Procedures: potential ear discomfort from loud noise and claustrophobia or fear of confined spaces, excessive anxiety.

3. **Infrequent Risks:**

4. **Other Risks:**
   Experimental Interventions: There is a potential risk of the strong magnetic field of the scanner attracting metallic objects toward the magnet. There are certain conditions that would exclude the subject from having a MR study. Follow up Procedures: There is a potential risk of the strong magnetic field of the scanner attracting metallic objects toward the magnet. There are certain conditions that would exclude the subject from having a MR study. These conditions include the presence or suspected presence of a heart pacemaker, aneurysm clip, ear implant, IUD, shrapnel or metallic fragments in or on the body or eyes, neuro-stimulators, or other metal devices. No other serious effects have been reported from being in the 1.5 Tesla magnet, although vertigo (e.g., dizziness and nausea) has been reported at higher field strengths. To minimize these risks, the subject will be carefully screened for metallic objects in their possession before entering the magnet room.

View: Pitt Risk

Risk

1. * **Research Activity:**
   Risks from reactions to anesthetic medicines

2. **Common Risks:**

3. **Infrequent Risks:**

4. **Other Risks:**
   Experimental Interventions: Some anesthetic medicines may cause allergic or other abnormal reactions in some people, but these are rare. If you suspect you may have such a problem, you should tell both your surgeon and anesthesia specialist well before your surgery. Testing will then be arranged as necessary. A rare, potentially fatal condition called malignant hyperthermia (MH) may be triggered by some anesthetics. The anesthetics most commonly associated with malignant hyperthermia include the inhalation anesthetics and the muscle relaxant medicines.

Risk

1. * **Research Activity:**
   Risk of Venipuncture (blood draw)

2. **Common Risks:**

3. **Infrequent Risks:**
   Screening Procedures: Infrequent (Occurs in 1% to 10% or 1 to 10 out of 100 people): mild pain and discomfort at the injection or needle insertion site as well as possible infection, bleeding, bruising and soreness. Experimental Interventions: Infrequent (Occurs in 1% to 10% or 1 to 10 out of 100 people): mild pain and discomfort at the injection or needle insertion site as well as possible infection, bleeding, bruising and soreness.

4. **Other Risks:**
   Screening Procedures: Rare (Occurs in less than 1% or less than 1 out of 100 people): severe pain; swelling; possibly an infection from the actual injection; fainting. Experimental Interventions: Rare (Occurs in less than 1% or less than 1 out of 100 people): severe pain; swelling; possibly an infection from the actual injection; fainting.

View: Pitt Risk

Risk

1. * **Research Activity:**
   Physical therapy evaluations

2. **Common Risks:**

3. **Infrequent Risks:**

4. **Other Risks:**
   During strengthening and stretching protocols, there is a risk that the patient may experience muscle discomfort/ pain, muscle strain, or fatigue. These risks will be minimized by providing detailed explanations and demonstrations of all exercises and interventions prior to any participant activity, allowing all activities to be voluntary and able to be stopped at any time, including optional rest periods, initial supervision and spotting of all participants. Spotting will be performed by trained therapists. In the case of a fall, participants will be immediately evaluated by a therapist who has been trained in determining the level of severity of potential injury, and in the event of injury, one of the physician investigators associated with this study will be notified immediately by telephone so the situation can be described and his/ her recommendation for further care can be followed. Any emergency medical care, if needed, will be sought at the local hospital. Subjects will be informed that they will need to communicate any discomfort that they experience during physical therapy evaluation session

View: Pitt Risk

Risk

1. * **Research Activity:**
   Risks of Electromyography (EMG):

2. **Common Risks:**
   Experimental Interventions: People usually have a small amount of discomfort during EMG testing because of pin insertion. Disposable needles are used so there is no risk of infection. During nerve conduction studies, small electrodes are taped to the skin. Follow up Procedures: People usually have a small amount of discomfort during EMG testing because of pin insertion. Disposable needles are used so there is no risk of infection. During nerve conduction studies, small electrodes are taped to the skin or placed around fingers. The subject typically experience a brief and mild shock, which may be a bit unpleasant. Most people find it only slightly annoying.

3. **Infrequent Risks:**

4. **Other Risks:**

Risk

1. * **Research Activity:**
   Surgical Anesthesia

2. **Common Risks:**
   Although all types of anesthesia involve some risk, major side effects and complications from anesthesia are uncommon. Your specific risks depend on your health, the type of anesthesia used, and your response to anesthesia. Some people who are going to have general anesthesia express concern that they will not be completely unconscious but will "wake up" and have some awareness during the surgical procedure. Awareness during general anesthesia is very rare because anesthesia specialists devote careful attention and use many methods to prevent this.

3. **Infrequent Risks:**
   General anesthesia suppresses the normal throat reflexes that prevent aspiration, such as swallowing, coughing, or gagging. To help prevent aspiration, an endotracheal (ET) tube may be inserted during general anesthesia. When an ET tube is in place, the lungs are protected so stomach contents cannot enter the lungs. Aspiration during anesthesia and surgery is very uncommon. To reduce this risk, people are usually instructed not to eat or drink anything for a specific number of hours before anesthesia so that the stomach is empty. Anesthesia specialists use many safety measures to minimize the risk of aspiration. Insertion or removal of airways may cause respiratory problems such as coughing; gagging; or muscle spasms in the voice box, or larynx (laryngospasm), or in the bronchial tubes in the lungs (bronchospasm). Insertion of airways also may cause an increase in blood pressure

4. **Other Risks:**
   These include changes in blood pressure or heart rate or rhythm, heart attack, or stroke. Death or serious illness or injury due solely to anesthesia is rare and is usually also related to complications from the surgery. Death occurs in about 1 in 250,000 people receiving general anesthesia, although risks are greater for those people with serious medical conditions. Serious side effects of general anesthesia are uncommon in people who are otherwise healthy. But because general anesthesia affects the whole body, it is more likely to cause side effects than local or regional anesthesia. Most side effects of general anesthesia are minor and can be easily managed.

View: Pitt Risk

Risk

1. * **Research Activity:**
   Risk of Chest X-ray

2. **Common Risks:**
   Experimental Interventions: The chest x-ray is one of the lowest radiation exposure medical examinations performed today. The effective radiation dose from this procedure is about 0.1 mSv, which is about the same as the average person receives from background radiation in 10 days.

3. **Infrequent Risks:**

4. **Other Risks:**

View: Pitt Risk

Risk

1. * **Research Activity:**
   CT Scan-Risks of Radiation Exposure

2. **Common Risks:**
   Study Procedures: This study will involve exposure to radiation. The amount of radiation exposure that each patient will receive will be about 1.3 rem per scan (a total of 5.2 rem) with minimum exposure of other areas of the body. There is no minimum amount of radiation exposure that is recognized as being totally free of the risk of causing genetic mutations or cancer. However, the risk associated with the amount of radiation exposure is felt to be low and comparable to everyday risks. All female study participants will be tested for pregnancy using a dip stick test to verify they are not pregnant prior to all CT scans being obtained and results will be recorded to the research chart.

3. **Infrequent Risks:**

4. **Other Risks:**

Risk

1. * **Research Activity:**
   Ultrasound guided biopsy

2. **Common Risks:**
   Bleeding: It is possible, though unusual to experience a bleeding episode during or after this procedure. Bruising may result after the biopsy due to capillary interruption, Redness, swelling, pain may result from the biopsy site post procedure

3. **Infrequent Risks:**
   In rare cases: Infection is unusual after this biopsy procedure, should infection occur additional treatment including antibiotics or surgery may result. Scar: the skin when healing occurs at the biopsy area may result in scar In rare cases: Infection is unusual after this biopsy procedure, should infection occur additional treatment including antibiotics or surgery may result. Scar: the skin when healing occurs at the biopsy area may result in scarring.

4. **Other Risks:**
   hematoma, nerve injury, infection at biopsy site. Risk of nerve or vessel damage, due to alterations in the anatomy of this type of injury.

View: Pitt Risk

Risk

1. * **Research Activity:**
   Risk of Breach of Confidentiality

2. **Common Risks:**

3. **Infrequent Risks:**

4. **Other Risks:**
   Study Procedures: Participation in this research study does involve the potential risks of a breach of confidentiality of the medical record information and associated privacy of the participants. The study investigators will take steps to reduce these risks by: 1) removing direct participant identifiers (i.e., names, social security numbers, medical record numbers) from information stored in the study records; 2) securing, in a separate location, and limiting access to information linking codes assigned to the study record information with direct participant identifiers; and 3) limiting access to information contained within the study records to study investigators only.

Risk

1. * **Research Activity:**
   Surgical procedure with Xenmatrix AB™

2. **Common Risks:**

3. **Infrequent Risks:**

4. **Other Risks:**
   Soft tissue repair is surgery, and with any surgery there may be general adverse effects or complications: • Infection after the implantation of the device could cause death or loss of limb. • The compromised skin may not heal from the surgery and amputation may be necessary. • The reconstruction may not take making the condition worse than it was before the surgery. • The muscle may be destroyed, and may never work again, regardless of the surgical outcome of the repair. • Injury to nerves and blood vessels • Fractures • Weakness • Stiffness or instability of the joint • Pain/Tenderness at the site • Scarring • Inability to repair a tendon • Re-rupture • pneumonia • cardiovascular disorders, sterile abcess and • General risks associated with surgery and anesthesia • Additional surgery as standard of care in the event of an adverse event. Additional surgery(ies) is/are considered standard of care procedures to address drain removal, hematoma development, infection, or other complications as anticipated with surgical procedures. PIs will follow protocol for the research surgery and treat complications as required by standard of care guidelines for post-operative complications. There are also a few related risks associated with the implantable device: • Stretching or tearing of the implant • Stiffness • Chronic inflammation or swelling • Longer rehabilitation period • Failure of the implant to be replaced by natural tissue • Immunological reaction • change in position or loosening of the components, • dislocation, • hematoma, • Allergic reactions or rejection of the material could occur, particularly if you have a history of multiple or severe allergies to antibiotics Rifampin and Minocycline or hypersensitivity to tetracycline or other components of the device, or have an overly sensitized immune system, or a sensitivity to pork products. Careful consideration should be used in the use of this device in with patients with compromised hepatic function.

View: Pitt Risk

Risk

1. * **Research Activity:**
   Risks of Electrocardiogram (EKG):

2. **Common Risks:**
   Experimental Interventions: It is common (Occurs in 10-25% of people (10 to 25 out of 100 people) that you may experience irritation or redness at the sites where small adhesive disks are placed on the chest skin to hold the wires that are hooked to the computer that measures heart rhythm.

3. **Infrequent Risks:**

4. **Other Risks:**

UNIVERSITY of PITTSBURGH
Department of Plastic Surgery

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: "XENMATRIX™ AB Surgical Graft for the repair of severe musculotendinous tissue damaged by trauma"

KEY INFORMATION

You are being asked to take part in a research study. Research studies include only people who choose to take part. The study team members will explain the study to you and will answer any questions you might have. You should take your time to make your decision.

- The purpose of the study is to examine the ability of XENMATRIX™ AB Surgical Graft to restore your muscle cells in the area of your injury. It is also to assess the muscle tissue repair procedure to identify what helps the graft to work and whether you regain function in the muscle that is affected.
- The study will last for approx. 9-11 months. There will also be up to a four month (16 week) period while you will have physical therapy between your initial visit and your surgery. This also includes a 6-month post-surgical follow-up period including preoperative training, a preoperative visit, a surgical visit, and 5 postoperative visits. 30 subjects will be recruited for the study, with 10 subjects undergoing the surgical procedure.
- The study will involve a procedure to be added to the standard surgical procedure, that will include the XENMATRIX™ AB Surgical Graft followed by a course of physical therapy
- Risks of the XENMATRIX™ AB Surgical Graft include:
    - Stretching or tearing of the implant
    - Stiffness
    - Chronic inflammation or swelling
    - Longer rehabilitation period
    - Failure of the implant to be replaced by natural tissue
    - Allergic reaction which could require removal
    - Change in position or loosening of the components
    - Dislocation
    - Hematoma – an area of bleeding inside the body at the surgical site
    - Allergic reactions or rejection of the material could occur, particularly if you have a history of multiple or severe allergies to antibiotics, Rifampin and Minocycline or hypersensitivity to tetracycline or other components of the device, or have an overly sensitized immune system, or a sensitivity to pork products.
- You may or may not personally benefit from your participation in this study. There is the

possibility that you may experience improvements in limb function; however, there is no guarantee that you will receive such a benefit. This study may help us to understand how surgeries that use extracellular matrix material have an effect on muscle/tendon changes following surgery.

- If you decide not to participate in this experimental study, there are several other treatments or procedures you may wish to consider:
  - Getting reconstructive surgery without being in this, or any, study
  - Participating in another study
  - No additional surgical treatment

Any findings by the research team during your participation that could affect your usual medical care will be given to you by the study physician.

PRINCIPAL INVESTIGATOR:

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Source of Support: Department of Defense

Why is this research being done?
We are conducting a clinical trial to assess the effectiveness of XENMATRIX™ AB Surgical Graft in the restoration and repair of muscle loss after trauma. The study has several goals:

1. Study the ability of XENMATRIX™ AB Surgical Graft to restore both how well your muscle works and how strong it is
2. See what infections occur with the use of the XENMATRIX™ AB Surgical Graft. The graft has an antibiotic coating, specifically, Rifampin and Minocycline
3. To examine the properties of your muscle cells and tissues in the area that is repaired to see if there are things that identify what helps the graft work and how you gain function in the muscle that is affected.

If you qualify to be in this study, during your surgery, you will receive a material made of an extracellular matrix (ECM) (a material that lays a framework to provide structural support for cells to grow on). In this study, this Food and Drug Administration (FDA)-approved ECM device (XENMATRIX™ AB) will be used during the surgery. The operative procedure and implanting of the device for this study is a research procedure. The ECM substance has been approved by the FDA as an implantable device and is made from porcine (pig) tissue and composed mostly of collagen (a naturally occurring protein in our bodies).

How long will I be in this research?
The goal of this research study is to see how each person's injuries heal over time, and to measure changes in the functional ability of the repaired limb during a 6-month post-surgical follow-up period. The study will last for approximately 9-11 months. There will be a four month period where you will have physical therapy between your initial visit and your surgery. We will enroll 10 subjects in this study.

What treatments or procedures are available if I decide not to take part in this research study?
If you decide not to participate in this experimental study, there are several other treatments or procedures you may wish to consider:

- Getting reconstructive surgery without being in this, or any, study
- Participating in another study
- No additional surgical treatment

What procedures will be performed for research purposes?
If you decide to participate in this study, we will do some or all the following tests to see if you are eligible for the study. The following procedures will be completed after you have discussed the study with your physician and signed the informed consent. These procedures are research; neither you nor your insurance company will be billed for these procedures. These procedures may occur over several sessions and at different locations within the UPMC system.

Screening Visit:
All screening procedures will be performed at the UPMC Aesthetic Plastic Surgery Center in a private room and at the UPMC Montefiore and Presbyterian University Hospitals. These screening procedures will take approximately 3.5-4 hours and may occur on different dates.

We will collect the following information for research purposes. If you agree to participate, you will be asked to complete the following research procedures to determine if you are eligible:

- Review of medical records related to injury, past surgeries, health care, and medications. This will also include recording of demographic information (relationship status, education level, and employment status)
- Medical history and physical exam
- Collection of your medication profile
- Basic vital sign measurements (such as blood pressure, pulse, temperature)
- Blood tests: approximately 3 teaspoons will be obtained for blood counts, chemistry panel (test to check how well your kidneys and liver are working), and electrolytes.
- Tests to evaluate your injury:
    - CT scans, (sometimes called a CAT Scan) a large x-ray machine that looks like a donut, and generates a more detailed, cross sectional picture
    - MRI scan, which is an imaging test that uses powerful magnets and radio waves to create pictures of the body
    - Similar standard clinical tests
- Electromyography (EMG) to measure the electrical activity of muscles. This can also be referred to as nerve conduction velocity. This is done by inserting very thin needle electrodes through the skin into the muscle. The signals from the needles are translated into graphs, sounds or numbers that are then interpreted by a specialist.
- Physical therapy evaluation of affected area
- Pregnancy test (for women of childbearing potential)

Pre-Operative Physical Therapy Training Sessions:
If you qualify for this study, you will complete a series of physical therapy training sessions, which may last up to 16 weeks. This will be followed by a preoperative visit, prior to the surgery.

- These physical therapy sessions will be completed with you, specific to your needs, based on the physical therapist's assessment of your injury. The treatment plan for this physical training will maximize your strength and motion in your affected limb.
- Following completion of the physical therapy, you will return to UPMC's Aesthetic Plastic Surgery Center for the preoperative visit during which you will repeat many of the tests, listed above, that were first done during your eligibility screening.

Pre-Operative Visit 1
After all screening procedures have been completed and reviewed by investigators, you may need to

return to the Aesthetic Plastic Surgery Center for a brief follow up/exam or review of screening information. The following procedures will be performed:

- Review of medical records related to injury, past surgeries, health care, and medications
- Performance of a limited/brief medical history review and physical
- Collection of your medication profile, vital signs, and weight to calculate BMI measurement
- Pre-operative blood tests will be performed by laboratory personnel located on the 5th floor of the UPMC Montefiore building or on the 1st floor of UPMC Presbyterian and collection of a routine urinalysis. A total of approximately 2-3 teaspoons of your blood will be collected for this time point and processed to evaluate safety prior to the operative procedure.
- All female participants who are of childbearing potential will receive a urine pregnancy dip test.
- Physical therapy evaluations and assessments for function testing
- EKG (Electrocardiogram—a test that traces the electrical activity of your heart) will be performed if determined as medically necessary by a study physician
- Chest X-ray (will be performed if determined as medically necessary by a study physician)
- Assessment of adverse events

Should a clinically significant and/or unexpected disease or condition be found during these screening procedures, the research team will notify you and, with your permission, discuss those findings with your primary care physician for further evaluation.

Operative Visit

This operative procedure will take place at Magee Womens or Shadyside Hospital. One of the nurses from the surgical team will telephone you the night before the surgery and review your medications, time to arrive at the hospital and advise you not to have anything to eat or drink for approximately 12 hours before the surgery. The day of the surgery, someone from the Anesthesia Department will meet with you. You will be given general anesthesia, so that you will be unconscious during the surgery (you will not feel or remember anything that happens). Generally, surgery patients will be given a combination of drugs through a vein in their arm and/or gases that they will breathe through their nose. You will be given a separate consent document to sign for the surgery – which is a standard clinical procedure, and both the anesthesiologist (doctor who administers anesthesia) and surgeon will go over the risks of this surgery. The surgical procedure will take approximately 3 to 3.5 hours to complete. Once the surgical soft tissue area is identified, we will obtain a biopsy. This is a collection of a small amount of tissue, approximately the width of a pencil point from the muscle. We will use this sample to look at the tissue structure and cells. The muscle and/or tendon will then be repaired with placement of stitches and reinforced by sewing the ECM material in place. The ECM material being used is approved by the FDA for this purpose.

Post-Op Care/Monitoring: You will be cared for by qualified nursing staff of UPMC Magee Womens or Shadyside Hospitals post-anesthesia care unit following the surgical procedure. The nursing staff will closely monitor your overall condition. Prior to being discharged home, you will receive instructions on how to examine the site at home. You will also be given instructions on how to contact the

surgeon if you any excessive swelling, drainage, redness, fevers, severe changes in pain or sensation or any other problems once you are discharged from the hospital.

Following surgery, you may be required to stay in the hospital for up to 72 hours for observation and immediate post-surgical assessments. The doctor who performed your surgery will determine when you are discharged from the hospital. You will be given a pain log with instructions to begin collection on post-operative day one (even if still hospitalized) and to continue through Postoperative visit 3 (month 1). You will record your level (rate it) and type of pain (describe it), anything you do to relieve your pain and the results of your actions to relieve the pain. This will be recorded for each episode of pain. You will be instructed to bring all forms to the post-operative office visits beginning at the 3-6 day visit until your post-operative 3 visit. Prior to leaving the hospital, you will be given postoperative instructions and follow up appointments to return to the surgical outpatient clinic. You will be discharged from the hospital with prescription pain medication per standard of care.

Post-operative physical therapy training sessions:
As part of this study, you will also complete a series of post-operative physical therapy training sessions. You will begin your post-operative physical therapy sessions once you have been evaluated by your doctor and have been deemed ready. These sessions will last up to approximately 6 months with the frequency of these sessions to be determined by the physical therapy professional. This training is an individualized program based on your injured limb and is similar to the pre-operative training. The post-operative training will include instruction of exercise for you to perform at home.

Pain log form

- You will be given a pain log form with instructions on how to complete to record level and type of pain you experience, what is done for your pain, and outcomes for each episode of pain. You will be asked to bring these forms to each follow-up visit.

Post-Operative Visits:
You will also complete a series of medical follow-up visits in the weeks and months following surgery. A detailed schedule of these visits will be provided to you, but over a 6-month period, you can expect to make approximately 5 visits, each of which will require approximately 1.5 to 3 hours of your time; some post-operative visits may occur over several sessions. These visits may include a physical examination, review of medical history with a discussion of medications and any discomfort or problems.

Clinical Post-Operative Visit 1 (3-6 days):
You will return to UPMCs Aesthetic Plastic Surgery Center after the surgery for completion of the following research procedures. The total length of time of this visit is approximately 0.5-1.5 hours:

- Performance of a limited history and physical exam
- Collection and review of pain log (1-10 analog scale). Review monitoring instructions to continue monitoring and bring in pain log at post-operative visit 2

- Collection of your medication profile and vital signs
- Adverse event reporting
- External staples/sutures may be removed

Post-Operative Visit 2 (7-14 days ± 2 days):
You will return to UPMCs Aesthetic Plastic Surgery Center following the surgical procedure for completion of the following research procedures. During the 7-14 day postoperative period, the study visit may occur over 2 days due to clinical safety (i.e. assessment of incision site, suture removal, drain pull, etc.). It is also possible that the safety visit and post-op visit 2 may be completed on the same day. The total length of time of this visit is approximately 1.5-2 hours:

- Performance of a limited history and physical exam
- Collection of your medication profile, vital signs, weight
- Collection and review of pain log. Review monitoring instructions (to continue monitoring until post-operative visit 3)
- Physical therapy evaluation and functional tests will be completed of the affected area, and an equivalent body area for comparison, if available
- Adverse event reporting

Post-Operative Visit 3 (30 days +/- 7 days):
You will return to UPMCs Aesthetic Plastic Surgery Center following the surgical procedure for completion of the following research procedures. The total length of time of this visit is approximately 2-2.5 hours:

- Performance of a limited history and physical exam
- Collection of your medication profile, vital signs, and weight
- Collection and review of pain log
- Physical therapy evaluation and functional tests will be completed of the affected area, and an equivalent body area for comparison, if available
- Adverse event reporting
- **Small core needle biopsy:** During visits 3 and 5 you may also have a small core needle biopsy (the removal of a sample of tissue from you for laboratory examination) of the affected tissue area to look at changes in your cells at the surgery site. This procedure will take place in the radiology department of Magee Womens Hospital or Presbyterian/Montefiore/Shadyside under ultrasound guidance. This procedure will be performed by a study doctor who will first numb the area with lidocaine, or a similar local anesthetic drug and a small hollow needle will be used to collect approximately 1-5 grams of tissue. These samples will be processed under the supervision of Stephen Badylak, DVM, PhD, MD, a co-investigator on this trial, within his laboratory located in McGowan Institute for Regenerative Medicine. The samples will be deidentified and labeled with a unique study number and stored for an indefinite period of time.

The samples may be used for this study and for other studies pertaining to the repair of muscle injuries. Whole genome sequencing will not be done on your specimens.

The study coordinator will call you within 72 hours after the (visit 3 or 5) biopsy procedure to ask you about any signs and symptoms you may have experienced after these procedures (examples of these could be bleeding or signs of infection, such as elevated temperature, redness or extreme tenderness at the site, drainage etc.).

Post-Operative Visit 4 (8-10 weeks +/-2 weeks): You will return to UPMCs Aesthetic Plastic Surgery Center after the surgical procedure for completion of the following research procedures. The total duration of this visit is approximately 1.5-2 hours:

- Performance of a limited history and physical exam
- Collection of your medication profile, vital signs, and weight
- Adverse event reporting
- Physical therapy evaluation and functional tests will be completed of the affected area, and an equivalent body area for comparison, if available

Post-Operative Visit 5 (24-28 weeks +/- 2 weeks):
You will return to UPMCs Aesthetic Plastic Surgery Center after the surgical procedure for completion of the following research procedures. The total length of time of this visit is approximately 2.5-3 hours:

- Medical record chart review
- Performance of a limited history and physical exam
- Collection of your medication profile, vital signs, and weight
- Adverse event reporting
- Physical therapy evaluation and functional tests will be completed of the affected area, and an equivalent body area for comparison, if available
- CT or MRI (dependent on if the affected limb has metal/shrapnel fragments intact) without contrast dye.
- EMG of operative limb area
- All female participants who are of childbearing potential will receive a urine pregnancy dip test. If the test result is positive the you will not continue participation in this research study.
- **Small core needle biopsy:** During visits 3 and 5 you may also have a small core needle biopsy (the removal of a sample of tissue from you for laboratory examination) of the affected tissue area to look at changes in your cells at the surgery site. This procedure will take place in the radiology department of Magee Womens Hospital or Presbyterian/Montefiore/Shadyside under ultrasound guidance. This procedure will be performed by a study doctor who will first numb the area with lidocaine, or a similar local anesthetic drug and a small hollow needle will

be used to collect approximately 1-5 grams of tissue. These samples will be processed under the supervision of Stephen Badylak, DVM, PhD, MD, a co-investigator on this trial, within his laboratory located in McGowan Institute for Regenerative Medicine. The samples will be deidentified and labeled with a unique study number and stored for an indefinite period of time. The samples may be used for this study and for other studies pertaining to the repair of muscle injuries. Whole genome sequencing will not be done on your specimens.

The study coordinator will call you within 72 hours after the (visit 3 or 5) biopsy procedure to ask you about any signs and symptoms you may have experienced after these procedures (examples of these could be bleeding or signs of infection, such as elevated temperature, redness or extreme tenderness at the site, drainage etc.).

Any findings by the research team during your participation that could affect your usual medical care will be given to you by the study physician.

Covid-19 testing:
There is a possibility that you may be asked to complete a test to determine your Covid-19 status at one of your research visits. One example of a situation where this would occur, is if you develop symptoms of Covid-19 after you have arrived in Pittsburgh. Also, at your pre-operative visit, you may be asked to complete a Covid-19 test prior to surgery.

There are two types of tests used to detect Covid-19, RT-PCR or Antigen tests. A RT-PCR test detects genetic material of the virus using a lab technique called reverse transcription polymerase chain reaction (RT-PCR). An antigen test detects certain proteins in the Covid-19 virus.

In both cases, a fluid sample is collected by inserting a long nasal swab into both your nostrils and taking fluid from the back of your nose to get a sample.

What are the possible risks, side effects, and discomforts of this research study?
As with any research or clinical procedure, there may be side effects that are currently unknown and these unknown risks could be permanent, severe or life threatening, or even cause death. You will be watched carefully for any side effects. You should inform your study doctor about any side affects you experience while taking part in the study.

Surgical procedure with XENMATRIX™ AB

- Infection after the implantation of the device could cause death or loss of limb.
- The compromised skin may not heal from the surgery and amputation may be necessary. The reconstruction may not take making the condition worse than it was before the surgery.
- The muscle may be destroyed, and may never work again, regardless of the surgical outcome of the repair.
- Injury to nerves and blood vessels
- Fractures

- Weakness
- Stiffness or instability of the joint
- Pain/tenderness at the site
- Scarring
- Inability to repair a tendon
- Re-rupture
- Pneumonia
- Cardiovascular Disorders
- Sterile abscess, which is a skin infection caused by something irritating the skin
- General risks associated with surgery and anesthesia
- Additional surgery as standard of care in the event of an adverse event.

Additional surgery(ies) is/are considered standard of care procedures to address drain removal, hematoma development, infection, or other complications as anticipated with surgical procedures. The principal investigator, Dr. Rubin will treat complications as required by standard of care guidelines for post-operative complications.

XENMATRIX™ AB Surgical Graft

- Stretching or tearing of the implant
- Stiffness
- Chronic inflammation or swelling
- Longer rehabilitation period
- Failure of the implant to be replaced by natural tissue
- Allergic reaction which could require removal
- Change in position or loosening of the components
- Dislocation
- Hematoma, an area of bleeding inside the body at the surgical site
- Allergic reactions or rejection of the material could occur, particularly if you have a history of multiple or severe allergies to antibiotics Rifampin and Minocycline or hypersensitivity to tetracycline or other components of the device, or have an overly sensitized immune system, or a sensitivity to pork products.

Please tell the study team if you have any history of problems with your liver. The graft should not be used in that case.

General Anesthesia affects the whole body and is more likely to cause side effects such as nausea and/or vomiting and sore throat, which are minor and can be easily managed.

Infrequent Risks:

- Aspiration during anesthesia and surgery is uncommon. Aspiration occurs when the anesthesia suppresses the normal throat reflexes such as swallowing, coughing, or gagging
- Insertion or removal of airways may cause respiratory problems such as coughing; gagging; or muscle spasms in the voice box, or larynx (laryngospasm), or in the bronchial tubes in the lungs (bronchospasm) and may cause an increase in blood pressure

(hypertension) and heart rate (tachycardia).

- Incorrect placement of the tube can cause hypoxia (lack of oxygen).
- Other complications may include damage to teeth and lips
- Swelling in the larynx, sore throat, and hoarseness, temporary or permanent vocal cord damage, drug reactions, and/or death.

Although all types of anesthesia involve some risk, major side effects and complications from anesthesia are uncommon. Your specific risks depend on your health, the type of anesthesia used, and your response to anesthesia.

Other Serious Risks of General Anesthesia Include:

- Severe drop in body temperature
- Changes in blood pressure or heart rate or rhythm, heart attack, or stroke.
- Death or serious illness or injury due solely to anesthesia is rare and is usually also related to complications from the surgery.

Reactions to Anesthetic Medicines:

- Some anesthetic medicines may cause allergic or other abnormal reactions in some people, but these are rare. If you suspect you may have such a problem, you should tell both your surgeon and anesthesia specialist well before your surgery. Testing will then be arranged as necessary.
- A rare, potentially fatal condition called malignant hyperthermia (MH) may be triggered by some anesthetics. The anesthetics most commonly associated with malignant hyperthermia include the inhalation anesthetics and the muscle relaxant medicines.

Electrocardiogram (EKG):

Common Risks: It is common (occurs in 10-25% of people) that you may experience irritation or redness at the sites where small adhesive disks are placed on the chest skin to hold the wires that are hooked to the computer that measures heart rhythm.

Electromyography (EMG):

- Common Risks: people usually have a small amount of discomfort during EMG testing because of pin insertion. Disposable needles are used so there is no risk of infection. During nerve conduction studies, small electrodes are taped to the skin. You typically experience a brief and mild shock, which may be a bit unpleasant. Most people find it only slightly annoying.

Ultrasound Guided Biopsy:

Common Risks:

- Bleeding: It is possible, though unusual to experience a bleeding episode during or after this procedure.
- Bruising may result after the biopsy due to capillary interruption; redness, swelling, pain may result from the biopsy site after surgery.

Infrequent Risks:

- Infection is unusual after a biopsy procedure; should infection occur additional treatment including antibiotics or surgery may result.
- Scar: the skin when healing occurs at the biopsy area may result in scarring in rare cases.

Other Risks: Hematoma/blood vessel damage, nerve injury that could result in numbness or hypersensitivity, which may or may not be permanent.

CT Imaging:

Common Risks: The amount of radiation exposure that you will receive from this CT scan is about 1.3 rem (rem is a unit of radiation exposure) to your affected limb, with minimum exposure of other areas of your body.
You will receive a total of 2.6 rems for the entire study. For comparison, radiation workers are permitted, by federal regulation, a maximum radiation exposure of 50 rems per year to any single body organ. The risk associated with the amount of radiation exposure that you will receive from taking part in this study is felt to be low and comparable to everyday risks.

In addition, if you are a female of childbearing potential participating in this study, you will be asked to have a urine dip stick pregnancy test to verify you are not pregnant prior to all CT scans being obtained. All results of this test will be recorded to your research chart.

Because CT scans require you to lay still or flat in a small confined space for a period of time, you may experience a feeling of becoming closed in or uncomfortable (claustrophobic). Should this experience occur, you can immediately contact the technician and stop the procedure.

MRI:

Common Risks: Potential ear discomfort from loud noise and claustrophobia or fear of confined spaces, excessive anxiety.

Other Risks: Certain conditions will exclude you from having a MR study, including the presence or suspected presence of a heart pacemaker, aneurysm clip, ear implant, IUD, shrapnel or metallic fragments in or on the body or eyes, neuro-stimulators, or other metal devices. Dental fillings do not present a problem with MRI. No other serious effects have been reported from being in the 1.5 Tesla magnet, although vertigo (e.g., dizziness and nausea) has been reported at higher field strengths. To minimize these risks, you will be carefully screened for metallic objects that are in your body or your possession before entering the magnet room. The MRI scans require you to lay still or flat in a small confined space for period of time, you may experience a feeling of becoming closed in or uncomfortable (claustrophobic). Should this experience happen, you can immediately contact the technician and stop the MRI scan.

Physical Therapy Evaluation Sessions:

Other Risks: During strengthening and stretching evaluations, there is a risk that you may experience muscle discomfort/ pain, muscle strain, or fatigue. These risks will be minimized by providing detailed explanations and demonstrations of all exercises prior to doing any activity, all activities are voluntary, and you will be able to stop at any time. We will include optional rest periods, supervision and spotting (safe standby of trained therapist personnel) during your activity. In the case of a fall, you will be immediately evaluated by a therapist who has been trained in understanding the level of severity of your potential injury, and in the event of injury, one of the doctors associated with this study will be notified immediately by telephone so the situation can be described and his/her recommendation for further care can be followed. Any emergency medical care, if needed, will be sought at the local hospital. You will be asked to inform the therapist of any discomfort that you may experience during physical therapy evaluation sessions.

Collection and Storage of Private Health Information and Biospecimens:

Your participation in this research study does potentially involve a risk of a breach of confidentiality of the medical record information and associated privacy. The study doctors will take steps to reduce these risks by: 1) removing direct participant identifiers (i.e., names, social security numbers, medical record numbers) from information stored in the study records; 2) securing, in a separate location, and limiting access to the codes that are assigned to your information with direct participant identifiers; and 3) limiting access to information contained within the study records to study doctors only.

Blood Draws:

- **Infrequent Risks:** (Occurs in 1% to 10% or 1 to 10 out of 100 people): mild pain and discomfort at the injection or needle insertion site as well as possible infection, bleeding, bruising and soreness. Experimental Interventions: Infrequent (Occurs in 1% to 10% or 1 to 10 out of 100 people): mild pain and discomfort at the injection or needle insertion site as well as possible infection, bleeding, bruising and soreness.
- **Rare**: (Occurs in less than 1% or less than 1 out of 100 people): severe pain; swelling; possibly an infection from the actual injection; fainting. Experimental Interventions: Rare (Occurs in less than 1% or less than 1 out of 100 people): severe pain; swelling; possibly an infection from the actual injection; fainting.

Chest X-ray:

Common Risks: The chest x-ray is one of the lowest radiation exposure medical examinations performed today. The effective radiation dose from this procedure is about 0.1 mSv, which is about the same as the average person receives from background radiation in 10 days.

Covid-19 Testing

Common Risks: include mild discomfort while the nasal swab is being collected.

If we learn of any new information about study risks that could cause you to change your mind about continuing to participate, we will notify you promptly.

What are the possible benefits from taking part in this research study?
You may or may not personally benefit from your participation in this study. There is the possibility that you may experience improvements in limb function; however, there is no guarantee that you will receive such a benefit. This study may help us to understand how surgeries that use extracellular matrix material may have an effect on muscle/tendon changes following surgery.

Alternative Treatments
You may seek treatment with your own health care team for surgical or medical management of your injured arm or leg. This may include alternative surgical procedures, rehabilitative services and / or both or no further or additional treatment. Your study investigator will discuss further with you during the consent process this information and if you desire, you may discuss with your healthcare team. The interventional device XENMATRIX™ AB surgical graft (C R BARD Inc.) is an approved medical device and is available to surgeons outside of study participation.

Will I or my insurance provider be charged for the costs of any procedures performed as part of this research study?
Some of the services or items in this study are part of the regular treatment for your condition. These would be performed or used even if you were not in this study. The costs for these services or items will be billed to your insurance. You will be responsible for any costs your insurance does not cover. If you have any questions about these costs, or what out-of-pocket expenses you may be responsible for, contact your insurance company. If you are uninsured, you will be responsible for these costs.

Neither you nor your insurance company will be charged for any research medical tests, surgery, or follow-up tests. All study procedures that are specifically being performed for this study (i.e., CT/MRI scans, collection of blood and research samples, questionnaires) are being covered under a contractual agreement with the Department of Defense. If you receive a bill or believe that your health insurance has been billed for something that is part of this research study, immediately notify a member of the research team or UPMC Patient Billing Services.

Please note, if your Covid-19 test is found to be positive, or you demonstrate symptoms of the virus while in Pittsburgh, your research visit may need to be cancelled. If this were to occur, your physician would treat you as clinically necessary for the virus, and your clinical care at UPMC may be charged to your insurance and/or to you.

Will I be paid if I take part in this research study?
You will receive reimbursement of $104.00 /day upon completion of each study visit conducted at the University of Pittsburgh Medical Center (UPMC). You will receive reimbursement of $104.00 /day only up to the first 48 hours of your surgical hospitalization and post op recovery period. This is intending to cover expenses (i.e. meals, parking, post-operative meds, tolls, etc.) which may be encountered and could be associated with your participation in this clinical trial. Your reasonable travel expenses

will be reimbursed at the federal rate of 0.58 / mile round trip, per visit or under certain circumstances round trip air fare coverage from your place of residence to the UPMC Aesthetic Plastic Surgery Center or UPMC hospital/facility may be covered, in lieu of round-trip mileage. The details of reimbursement will vary from person to person and will be discussed during this visit.

You will be reimbursed for your travel time to the physical therapy sessions, once a week. Physical therapy training session reimbursement will be provided at $20.00 /week, provided you complete the total weekly visits as ordered by the MD. No partial reimbursement will be provided for missed or incomplete weekly visits. All participant reimbursement will be provided through Vincent Payment Solutions processing, which is a reloadable debit card payment system.

Your data or tissue samples may lead to new inventions. If the investigators are able to develop new products from the research use of your tissue or biological sample, there are currently no plans to share with you any money or other rewards that may result from the development of these new products.

Who will pay if I am injured as a result of taking part in this research study?
If you believe that the research procedures have resulted in an injury to you, immediately contact Dr. Rubin or the study coordinator (see first page). Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. Thus, if there is a surgical complication that does not require emergency care, the costs are not covered by the research. Currently, there is no plan for any additional financial compensation. You waive no legal rights by signing this consent.

Who will know about my participation in this research study?
To protect the confidentiality of information we obtain from you and your medical records, we will keep all information about you in a secure location. All paper records that could identify you will be stored in locked file cabinets, and all electronic records will be stored in password-protected files. Access to this information will be limited to research team members and to those health care professionals who are providing clinical services as part of this research study.

Will this research study involve the use or disclosure of my identifiable medical information?
As part of this study, we are also requesting your permission to review your medical records to obtain past, current, and future medical information from hospital and other medical facilities. We will obtain information concerning your diagnosis, age, past medical history, diagnostic or surgical procedures, prosthetic history and results of the tissue biopsy and blood tests that may have been done as part of your care. Should we receive this information, we may use this information to determine whether you meet the conditions for participation in this study, to compare your earlier test results to the findings from this study and, if possible, to use your previous exam results in place of or in addition to some of the exams needed for this study.

Although we will do everything in our power to protect your privacy and the confidentiality of your records, just as with the use of your medical information for health care purposes, we cannot guarantee the confidentiality of your research records, including information that we obtained from your medical records. This research study will result in identifiable information that will be placed into your medical records held at UPMC, including this consent form. The nature of the identifiable information resulting from your participation in this research study that will be recorded in your medical record will be derived from the medical/surgical (surgical procedure). Psychiatric interview information will be entered into the medical record only if it is important to ensure your medical/physical safety.

Who will have access to identifiable information related to my participation in this research study?
This identifiable information will be made available to members of the research team for an indefinite period of time. That medical information, as well as information obtained during this research study, may be shared with other groups, possibly including authorized officials from the FDA, Department of Defense, the University of Pittsburgh Office of Research Protections, the independent Medical Monitor for the study, who in turn may share with the US Army Medical Research and contracted entities for the purpose of monitoring the study and safety of participants. Authorized representatives of the UPMC hospitals or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) assessing internal hospital operations (i.e. quality assurance). Any information that is entered into your medical records will be available to you, in accordance with the UPMC Notice of Privacy Practices.

Your doctor may also be involved as an investigator in this research study, but you are not under any obligation to participate in any research study offered by your doctor. Before agreeing to participate in this research study, or at any time thereafter, you may wish to discuss participation in this study with another health professional, to obtain a 'second opinion' about study participation.

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by US Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Is my participation voluntary?
Your participation in this research study is completely voluntary. Whether or not you participate in this research study, it will have no effect on your current or future relationship with the University of Pittsburgh, UPMC or its affiliated health care providers or health care insurance providers.

May I withdraw, at a future date, my consent for participation in this research study?

You can, at any time withdraw from this research study; you can also withdraw your authorization for us to use your identifiable medical information for the purposes described above. This means that you will also be withdrawn from further participation in this research study. Any identifiable research or medical information obtained as part of this study prior to the date that you withdrew your consent will continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw from this research study, you should provide a written and dated notice of this decision to the principal investigator of this research study, Dr. J. Peter Rubin (412-383-8080) at the address listed on the first page of this form or his research colleagues. Your decision to withdraw your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider. If you decide to withdraw from study participation after you have received the study agent, you will receive standard-of-care treatment as applicable and have follow-up assessments collected to ensure your safety upon termination from study participation.

If I agree to participate in this research study, can I be removed from the study without my consent?

If the investigators feel that you cannot complete the study requirements safely (for example, positive pregnancy test, experience severe side effects, unable to complete physical therapy), they may withdraw you from the study. At the time of your withdrawal, the investigator will discuss with you the appropriate and requested follow up based on the specific event.

OPTIONAL CONSENT FOR DIGITAL RECORDINGS OF PROCEDURES

The research team is requesting permission to digitally record (i.e. photography or video) any and all portions of your pre-operative, operative, and post-operative course of treatment. These may include, but not be limited to, videos of personal interviews, functional assessment testing and clinical exams or photos of follow up clinical course, etc. These digital recordings and/or photos may be used for medical education and training, publication, and media reports – and, in any mode of transmission, including and not limited to: print, email, television, internet, etc. There is always a small risk of breach of confidentiality when personal images are stored. Some recordings will remain identifiable (interviews). Regarding the use of these digital recordings for education, training, publication and storage purposes, you will not be identified by name, only by a unique code number. Your identifiable features in these photographs will be blacked out (i.e., eyes, facial features, tattoos etc.). Regarding the use of your digital recordings for media purposes, you may be identified by name, but permission from you will be obtained in a separate consent document prior to the recordings being obtained. You are not required to give this permission and can refuse at any time after giving consent to these digital recordings being obtained. You can still participate in this study without permitting these recordings.

I consent to the digital recording, as described above:

_____ _____

Participant's Signature Date

I **do NOT** consent to the digital recording:

_____ _____

Participant's Signature Date

VOLUNTARY CONSENT FOR STUDY PARTICIPATION

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any aspect of this research study during the course of this study, and that such future questions, concerns or complaints will be answered by a qualified member of the research team or by Dr. Rubin, at 412-383-8080. I understand that I may always request that my questions, concerns or complaints be addressed to Dr. Rubin. At any time, I may also contact the Human Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable. By signing this form, I agree to participate in this research study, and allow the use and disclosure of my medical record information for the purposes described above. A copy of this consent form will be given to me.

_____

Printed name of Participant

_____ _____

Participant's Signature Date / Time

INVESTIGATOR CERTIFICATION:

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions, concerns or complaints as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____

Printed Name of Person Obtaining Consent Role in Research Study

_____ _____

Signature of Person Obtaining Consent Date/Time