DEFENSE HEALTH AGENCY
MADIGAN ARMY MEDICAL CENTER
9040 JACKSON AVENUE
TACOMA, WASHINGTON 98431-1100

MCHJ-MOE-C 9 June 2023

MEMORANDUM FOR LTC Joseph Galvin, Principal Investigator at Madigan Army Medical Center

SUBJECT: Madigan Army Medical Center Institutional Review Board Approval of Research Protocol, "Investigating Orthobiologics After Platelet-Rich Plasma and Photobiomodulation Treatment of Knee Osteoarthritis" Protocol #223072

1. The subject protocol has been reviewed for compliance with applicable human subject protection regulations by the Madigan Institutional Review Board (IRB). The primary objective of the protocol is to compare the effects of 1) standard physical therapy, 2) physical therapy plus Platelet-Rich Plasma (PRP) 3) physical therapy plus Photobiomodulation (PBMT) and 4) physical therapy plus PRP and PBMT on the biological cascade of knee OA by using precision medicine techniques to examine orthobiologics (synovial and serum inflammatory and progenitor cells) during the management process. The IRB determined that the PRP is being used as standard of care in accordance with its approved labeling and the LiteCure, Therapy system, Model LTS-1500 is exempt from IDE regulations in accordance with 21 CFR 812.2(c)(2) and assessed the protocol as presenting greater than minimal risk to participants. The IRB also required minor corrections to the consent form which have been addressed by the PI and administratively approved by the IRB Office. There are no outstanding human research protections issues to be resolved.

2. The following documents have been reviewed and found to comply with applicable Federal, Department of Defense (DoD), Defense Health Agency (DHA) and Madigan human subject protection requirements:

Submission Components			
Form Name		Version	Outcome
EIRB Protocol Template		Version 1.3	Approved
Study Document			
Title	Version #	Version Date	Outcome
223072 Study Flyer Final IRB 11May23	Version 1.0	05/11/2023	Approved
SRC Stipulation Responses	Version 1.0	02/02/2023	Acknowledged
COI- Hager	Version 1.0	12/08/2022	Acknowledged
MAMC DCI Impact Statement	Version 1.0	null	Acknowledged
TeleRay EPHI Statement 2021	Version 1.0	null	Acknowledged
TeleRay BIA Analysis 2021	Version 1.0	null	Acknowledged
MAMC LSO Approval Memo	Version 1.0	null	Acknowledged
Department Chief LOS	Version 1.0	null	Acknowledged
McKee_Samantha_CITI_OUSD_RCR_Report_2025	Version 1.0	null	Acknowledged

10 30			
McKee_Samantha_CITI_OUSD_GCP FDA_Report_2025 10 26	Version 1.0	null	Acknowledged
McKee_Samantha_CITI_OUSD_Biomedical RC_Report_2025 10 25	Version 1.0	null	Acknowledged
McKee_Samathan_CV	Version 1.0	null	Acknowledged
COI - McKee	Version 1.0	null	Acknowledged
COI - Venturino	Version 1.0	null	Acknowledged
COI - Gillette	Version 1.0	null	Acknowledged
COI - Colburn	Version 1.0	null	Acknowledged
COI - Bastian	Version 1.0	null	Acknowledged
Appendix T Laser Operator Training Plan	Version 1.0	null	Acknowledged
Appendix S Biospecimen Master Key	Version 1.0	null	Approved
LiteCure Device Documents	Version 1.0	null	Acknowledged
LightForce Family of Products Brochure RevA	Version 1.0	null	Acknowledged
MAMC DPALS Impact Statement	Version 1.0	null	Acknowledged
COI - Lucio	Version 1.0	null	Acknowledged
Appendix I Chart Review CRF	Version 1.0	null	Approved
Appendix H Follow-Up Data Collection CRF	Version 1.0	null	Approved
Appendix E Activity, Pain, & Medication Log	Version 1.0	null	Approved
Appendix Q Injection Aftercare Handout	Version 1.0	null	Approved
COI - Free	Version 1.0	null	Acknowledged
COI - Schroeder	Version 1.0	null	Acknowledged
COI - Stormer	Version 1.0	null	Acknowledged
COI - Ory	Version 1.0	null	Acknowledged
COI - Metzger	Version 1.0	null	Acknowledged
COI - Galvin	Version 1.0	null	Acknowledged
Robert_Rossi_CV	Version 1.0	null	Acknowledged
Rossi_Robert_CITI_OUSD_RCR_Report_2025 08 14	Version 1.0	null	Acknowledged
Rossi_Robert_CITI_OUSD_GCP FDA_Report_ 2025 08 14	Version 1.0	null	Acknowledged
Rossi_Robert_CITI_OUSD_Biomedical RC_Report_ 2025 08 20	Version 1.0	null	Acknowledged
Karikari_Nana-king_CV	Version 1.0	null	Acknowledged
Karikari_Nana-king_OUSD_RCR_Report_2025 08 30	Version 1.0	null	Acknowledged
Karikari_Nana-king_OUSD_GCP FDA_Report_2025 08 31	Version 1.0	null	Acknowledged
Karikari_Nana-king_OUSD_Biomedical RC_Report_2025 08 25	Version 1.0	null	Acknowledged

COI - Karikari	Version 1.0	null	Acknowledged
Appendix B Intake CRF	Version 1.0	null	Approved
Appendix J Study Completion CRF	Version 1.0	null	Approved
Appendix O Screening Log	Version 1.0	null	Approved
Appendix R USU REDCap Overview	Version 1.0	null	Acknowledged
223072 Galvin Partial HIPAA Waiver - Signed	Version 1.0	null	Approved
MAMC PAO Impact Statement	Version 1.0	null	Acknowledged
MAMC Radiology Impact Statement_2022 10 03	Version 1.0	null	Acknowledged
Appendix G CBC Results CRF	Version 1.1	01/31/2023	Approved
Appendix F Study Treatment Documentation Log	Version 1.1	01/31/2023	Approved
Appendix D Baseline Data Collection CRF	Version 1.1	03/30/2023	Approved
Appendix A Inclusion Exclusion CRF	Version 1.2	03/30/2023	Approved
Appendix N Screening Script	Version 1.2	03/30/2023	Approved
Appendix C Demographics CRF	Version 1.1	03/30/2023	Approved
Appendix K Data Collection Schedule	Version 1.1	01/31/2023	Approved
Appendix L Study Flow Diagram	Version 1.1	02/01/2023	Approved
COI - Rossi	Version 1.1	null	Acknowledged
Roles & Responsibilities Log	Version 1.2	null	Acknowledged
Appendix P Master List	Version 1.1	null	Approved
Study Master Consent Form			
Title	Version #	Version Date	Outcome
223072 Galvin Consent wHIPAA Final IRB 30May23	Version 1.3	05/15/2023	Approved

3. The protocol is approved for a one-year period, 11 May 2023 – 10 May 2024. In accordance with 32 CFR 219.109(e) the protocol must be reviewed for continuation by the Madigan IRB by the expiration date: 10 May 2024. EIRB will attempt to send you reminders, however, submission of the continuing review report is your responsibility. Failure to submit the report on time will result in expiration of the IRB approval for your protocol and a requirement to cease all research activities. Submission of your continuing review report is due 60 days prior to the expiration date.

4. The protocol is approved to enroll up to 200 Active Duty Soldiers.

5. The IRB approved consent form with embedded HIPAA has been approved and stamped in EIRB. It is your responsibility to log into EIRB and print this version of your consent form for use during the consent process; the stamp is found on the last page (stamped Approved 30 May 2023; Expiration 10 May 2024). Federal regulations also require each participant receive a copy of the consent document.

6. The request for a partial waiver of HIPAA Authorization to use or disclose protected health information (PHI) for research has been approved by the Madigan IRB Madigan Army Medical Center (MAMC) IRB on 11 May 2023 and stamped as approved in EIRB, in accordance with

DOD 6025-18-R, C7.9.1 and 45 CFR 164.152 (i) (2) (ii)(A) – (C), as 1) the use or disclosure of PHI involves minimal risk to the privacy of the individuals, 2) the research could not practicably be conducted without the waiver or alteration and 3) the research could not practicably be conducted without access to and use of the protected health information.

7. One (1) study recruitment flyer (stamped/dated 11 May 2023) has been issued for your use. Please note that only the IRB stamped version of this flyer may be used in accordance with the IRB approved protocol and the advertising plan approved by the Public Affairs Officer, Madigan Army Medical Center.

8. **FUTURE USE** As a reminder this protocol was approved with a request for the retention of data collected for future use; this protocol approval is NOT an approval for that future use. To use the data retained for future use a separate request for that use must be submitted and approved prior to using any of those data.

9. Your study may require a Data Sharing Agreement (DSA) in accordance with DoDM 6025.18 and DoDI 8580.02. Send the following documents to the Defense Health Agency (DHA) Privacy & Civil Liberties Office (PCLO) for review to determine if a DSA is required, dha.ncr.j-6.mbx.dsa-mail@health.mil.

a. IRB Approval Letter (this letter)
b. EIRB Protocol v.1.3
c. IRB Approved Consent Form with Embedded HIPAA Authorization
d. IRB Approved Partial HIPAA Waiver of Authorization

10. Any modifications (including, but not limited to, changes in the principal investigator, inclusion/exclusion criteria, number of subjects to be enrolled, or procedures) must be submitted via a Modification Form in EIRB for Madigan IRB's review and approval prior to implementation.

11. Any deviation to the protocol that may have an effect on the safety or rights of the subject or the integrity of the study must be reported to the Madigan IRB as soon as the deviation is identified. The deviation must be reported via a Reportable Event Form in EIRB.

12. Unanticipated problems involving risk to subjects or others and all serious adverse events must be promptly reported to the Madigan IRB within 3 business days by telephone 253-968-0149 or by email sandra.l.smith399.civ@health.mil. A complete written report should be submitted in EIRB using the Reportable Event Form following the initial notification.

13. A final protocol report must be submitted to the Madigan IRB via a Closure Form in EIRB.

14. For funded research projects; only the Contracting Officer/Grants Officer can authorize expenditure of funds. The Principal Investigator must not construe this correspondence as approval for any contract funding and shall comply with the following:

a. Notify the funding agency of IRB approval by providing the IRB Approval Letter, IRB Stamped Consent Form and any other supporting documents in accordance with the funding agencies policies (such as a "cover sheet"), for their review and final approval.

b. Contact the appropriate contract specialist or contracting officer regarding authorization

for expenditure of funds.

15. All publications, presentations or abstracts arising from this work must be cleared through appropriate publication clearance procedures.

16. The results of this protocol must be filed in the Defense Technical Information Center (DTIC) (http://www.dtic.mil/dtic/submit/submit.html) Enterprise Content Management System (ECMS) within 90 days of completion of the protocol. A completed SF-298 must accompany the submission.

17. The IRB point of contact for this review is Athena Rayner at 253-968-3524 or athena.m.rayner.civ@health.mil.

Signature applied by Walter James Sowden on 06/12/2023 02:37:00 PM CDT

WALTER J. SOWDEN, PhD
LTC, MS
Chair, Institutional Review Board
Madigan Army Medical Center

EIRB Protocol Template (Version 1.3)

1.0 General Information

***Please enter the full title of your study:**

Investigating Orthobiologics After Platelet-Rich Plasma and Photobiomodulation Treatment of Knee Osteoarthritis

***Please enter the Protocol Number you would like to use to reference the protocol:**

Photomedicine Project 11: Orthobiologics after PRP and PBMT in Knee OA Population
* This field allows you to enter an abbreviated version of the Protocol Title to quickly identify this protocol.

Is this a multi-site study (i.e. Each site has their own Principal Investigator)?

Yes

Does this protocol involve the use of animals?

○ Yes ◉ No

2.0 Add Site(s)

2.1 List sites associated with this study:

Primary Dept?	Department Name
◉	**P and R** - Madigan Army Medical Center (MAMC)

3.0 Assign project personnel access to the project

3.1 *Please add a Principal Investigator for the study:

Galvin, Joseph William, D.O. LTC

Select if applicable

☐ Student ☐ Site Chair
☐ Resident ☐ Fellow

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Colburn, Zachary Tyler, PhD
Associate Investigator
Gillette, Laurel H, M.S.

Associate Investigator
HAGER, NELSON ALLEN
Associate Investigator
Schroeder, Jeremy Daniel, DO LTC
Associate Investigator
Stormer, Jonathan David
Associate Investigator

B) Research Support Staff

BASTIAN, MARIT Kari, B.S. Cell and Molecular Biology
Team Member
Free, Katherine E
Team Member
Karikari, Nana-King Ahwoi
Research Coordinator
Lucio, Whitley B
Research Coordinator
MCKEE, Samantha Jade
Research Coordinator
Metzger, Elizabeth C
Research Coordinator
Ory, Rian Lyndzie, MS
Research Coordinator
Rossi, Robert M, MPH
Research Coordinator
VENTURINO, Jennifer Rebecca
Team Member

3.3 *Please add a Protocol Contact:

Galvin, Joseph William, D.O. LTC
HAGER, NELSON ALLEN
Karikari, Nana-King Ahwoi
Lucio, Whitley B
MCKEE, Samantha Jade
Metzger, Elizabeth C
Ory, Rian Lyndzie, MS
Rossi, Robert M, MPH

The Protocol Contact(s) will receive all important system notifications along with the Principal Investigator. (i.e. The protocol contact(s) are typically either the Protocol Coordinator or the Principal Investigator themselves).

3.4 If applicable, please select the Designated Site Approval(s):

Benavides, Jerome M, LTC
Department Chair

Add the name of the individual authorized to approve and sign off on this protocol from your Site (e.g. the Site Chair).

4.0 Project Information

4.1 * What department(s) will be associated with this protocol?

- Orthopedics
- Physical Medicine & Rehab
- Podiatry
- Physical Therapy
- Other

4.2 * Is the IRB of record for this study an IRB/HRPP that does NOT use EIRB? If Yes, complete the application according to the IRB/HRPP Determination.

If your Projects or Protocols are under the oversight of another IRB that does use EIRB, stop this submission and contact the core site and request an invitation as a performing site.

If your Project or Protocol is now being submitted for the first time to an IRB that does use EIRB, continue with this application and answer the questions to be reviewed by the IRB.

Answering yes means the board of record is an IRB that does NOT use EIRB.

○ Yes ◉ No

4.3 * Is this protocol research, expanded access, or humanitarian use device?

◉ Yes ○ No

4.4 * What type of protocol is this?

- ☐ Behavioral Research
- ☑ Biomedical Research
- ☑ Clinical trial (FDA regulated)
- ☐ Educational Research
- ☐ Expanded Access
- ☐ Humanitarian Use Device (HUD)
- ☐ Psychosocial Research
- ☐ Oral History
- ☐ Other

4.5 Are you conducting this project in pursuit of a personal degree?

○ Yes ◉ No

4.7 * Is this human subjects research? (As defined by 32 CFR 219) Human subject means a living individual about whom an investigator (whether professional or student) conducting research:
(i) Obtains information or biospecimens through intervention or interaction with the individual, and

uses, studies, or analyzes the information or biospecimens; or
(ii) Obtains, uses, studies, analyzes or generates identifiable private information or identifiable biospecimens.

(•) Yes ( ) No

4.8 * Do you believe this human subjects research is exempt from IRB review?

( ) Yes (•) No

5.0 Personnel Details

5.1 Does the Principal Investigator have a Permanent Change of Station (PCS) Date or Estimated Institutional Departure Date (EIDD)?

( ) Yes (•) No

5.2 List any Research Team members without EIRB access that are not previously entered in the protocol:

No records have been added

5.3 Are any Contractors or Subcontractors involved in this study? If yes, please list them and describe their role.

(•) Yes ( ) No

Name: (Last, First, M.I.)	Phone Number:	Email Address:	Associated Institution:
Karikari, Nana-king Role on Protocol: Research Assistant and Clinical Laser Safety Officer (CLSO)	253-228-7347	nkarikari@genevausa.org	The Geneva Foundation / MAMC
McKee, Samantha Role on Protocol: Research Assistant II	229-412-4567	smckee@genevausa.org	The Geneva Foundation / MAMC
Free, Katherine	Phone Number:	Email Address:	Associated Institution:

Role on Protocol: Research Laboratory Technician		kfree@genevausa.org	The Geneva Foundation / MAMC
Name: (Last, First, M.I.) Rossi, Robert Role on Protocol: Research Coordinaor	Phone Number: 551-404-1923	Email Address: rrossi@genevausa.org	Associated Institution: The Geneva Foundation / MAMC
Name: (Last, First, M.I.) Ory, Rian L. Role on Protocol: MIRROR Regulatory Affairs Manager	Phone Number: 909-904-5034	Email Address: rian.ory.ctr@usuhs.edu	Associated Institution: The Geneva Foundation / USUHS / MAMC
Name: (Last, First, M.I.) Lucio, Whitley B. Role on Protocol: MIRROR Sr. Regulatory Affairs & Data Manager	Phone Number: 202-375-8831	Email Address: whitley.lucio.ctr@usuhs.edu	Associated Institution: The Geneva Foundation / USUHS
Name: (Last, First, M.I.) Metzger, Elizabeth C. Role on Protocol: MIRROR /Photomedicine Scientific Program Manager	Phone Number: 252-562-2419	Email Address: emetzger@genevausa.org	Associated Institution: The Geneva Foundation / USUHS
Name: (Last, First, M.I.) Heger, Nelson Role on Protocol: Associate Investigator	Phone Number: 425-218-1833	Email Address: nelson.hager.ctr@usuhs.edu	Associated Institution: The Geneva Foundation / USUHS / MAMC

5.4

Will you have a Research Monitor for this study?

- ○ Yes
- ◉ No
- ○ N/A

6.0 Data/Specimens

6.1 Does the study involve the use of existing data or specimens only (no interaction with human subjects)?

○ Yes ◉ No

7.0 Funding and Disclosures

7.1 Source of Funding:

Funding Source	Funding Type	Amount
: Other USUHS Award Number HU00011920056	: Research Development Testing and Evaluation (RDT&E) funds Photomedicine to Enhance Military Medicine	300000

Total amount of funding:

300000

7.2 Do you or any other Investigator(s) have a disclosure of a personal interest or financial nature significant with sponsor(s), product(s), instrument(s) and/or company(ies) involved in this study?

○ Yes ◉ No

All personnel engaged in research must complete and attach a Conflict of Interest (COI) form.

8.0 Study Locations

8.1 Is this a collaborative or multi-site study? (e.g., are there any other institutions involved?)

◉ Yes ○ No

8.2 Study Facilities and Locations:

			FWA or DoD	Assurance		

Institution	Site Name	Site Role	Assurance Number	Expiration Date	Is there an agreement?	IRB Reviewing for Site
Army	MAMC	Lead site	FWA00003277	09/13 /2024	: IAIR	: RHC - P IRB
P&R	USUHS	Coordinating center	FWA00001628	09/14 /2024	: IAIR	: RHC - P IRB

Other:

Other Institution Site	Site Role	FWA or DoD Assurance Number	FWA or DoD Expiration Date	Is there an agreement?	IRB Reviewing for Site
No records have been added					

8.3 Are there international sites?

Attach international approval documents, if applicable, when prompted. Note: Ensure local research context has been considered

○ Yes ◉ No

8.4 Is this an OCONUS (Outside Continental United States) study?

○ Yes ◉ No

Select the area of responsibility:

Have you obtained permission from that area of responsibility? (This is a requirement prior to study approval)

○ Yes ○ No

9.0 Study Details

9.1 Key Words:

Provide up to 5 key words that identify the broad topic(s) of your study

Photobiomodulation, Photomedicine, Platelet Rich Plasma, Orthobiologics, Knee Osteoarthritis

9.2 Background and Significance:

Include a literature review that describes in detail the rationale for conducting the study. Include descriptions of any preliminary studies and findings that led to the development of the protocol. The background section should clearly support the choice of study variables and explain the basis for the research questions and/or study hypotheses. This section establishes the relevance of the study and explains the applicability of its findings

Musculoskeletal injuries remain the primary reason for outpatient visits and non-deployable and limited duty status amongst Active-Duty Service Members. The vast majority of these injuries occur in the lower extremities. The knee is the most common injury location amongst trainees and is the second most common injury location from road marching (Molloy, 2020). These knee

injuries commonly lead to post-traumatic knee osteoarthritis (PTOA), a disease where there is progressive loss of cartilage due to an uncharacteristic force applied to the knee, as compared to non-traumatic knee osteoarthritis (OA), which is a result of cartilage loss due to wear and tear without a clear underlying cause (Hsu, 2021). Over 20,000 cases of knee OA were identified in the Active Forces over a span of ten years, and are rising in incidence (Showery, 2016).

Current treatments for knee OA (post-traumatic and non-traumatic) include physical therapy (PT), bracing for unloading, oral pain relievers, and corticosteroid and hyaluronic acid injections. These treatments focus on reduction in symptoms, pain relief, and increasing function and quality of life. The cascading disease progression is not thought to be halted or reversed, resulting in a continuation of progressive symptomatology (Ng, 2012).

Platelet-Rich Plasma (PRP) is a product derived from a patient's own blood, where a blood sample is taken and then concentrated via centrifugation to provide an injectable high in platelets. This blood product high in platelet content is then injected back into the body at the site of injury (Arnoczky, 2013). Two recent meta-analyses showed that PRP is a promising treatment mechanism for longitudinally (6-12 months post procedure) reducing pain and increasing function as compared to placebo, hyaluronic acid, and steroids in patients with knee OA; PRP was also the superior treatment for pain at 3 months post procedure (Filardo, 2021, Migliorini 2021). PRP is both safe and effective (Cook, 2018) and research indicates it may preventively slow OA progression, although the mechanism of action is not fully understood (Rodriguez-Merchan, 2013). PRP is theorized to reduce inflammatory, pro-angiogenic humoral and cellular immune responses, and increase cartilage anabolism while decreasing catabolism, via growth and nuclear factors. The exact cascade, however, is not thoroughly studied in humans, with most research originating from animal model studies (Dhillon, 2017; Huang, 2018). Overall, optimization of PRP treatment and understanding of the PRP biological pathway of action needs to be established in humans (O'Connell, 2019; Bansal, 2021). More work is also needed to understand the potential ability for PRP to slow or reverse OA degeneration.

In contrast, photobiomodulation therapy (PBMT) is a noninvasive treatment where a device that emits low level lasers is applied to the affected area to enhance recovery (Dompe, 2020). PBMT is a promising treatment for knee OA; a recent meta-analysis showed PBMT increases function and decreases stiffness and pain at rest and during activity (Rayegani, 2017), as compared to placebo. Another meta-analysis also confirmed the ability of PBMT to reduce pain and disability (Stausholm, 2019) in a knee OA population. Moreover, PBMT is effective in decreasing pain and increasing functionality in knee OA patients with or without therapeutic exercises (Paolillo, 2018). Low-level laser therapy in the management of knee arthritis has also shown to decrease the need for surgery (Ip, 2015). The exact application and dosage of PBMT for knee OA, however, still need to be refined (Rayegani, 2017).

PRP is postulated to increase chondrocyte proliferation, and increased collagen II and prostaglandin. Moreover, it may decrease apoptosis via insulin-like growth factor 1 (IGF-1). Inflammation reduction is also noted through regulated nuclear factor kappa B (NF-kB), cyclooxygenase-2 (COX-2), and reducing IL-1ß and tumor necrosis factor-alpha (TNF-a) (Dhillon, 2017). PBMT acts in an anti-inflammatory mechanism by reducing mediators such as (TNF-a) (Hamblin, 2007) and anti-inflammatory mediators such as IL-10 (Peplow, 2011). Taken together, PRP acts through pathways, including inflammation reduction, which PBMT is shown to reduce. The combination of the adjunctive therapies may increase this ant-inflammatory cascade.

In knee OA rat models, PBMT has shown to decrease osteoarthritic degeneration, indicated by less irregularities in chondrocytes (Assis, 2016), higher thickness, and a better Osteoarthritis Research Society International (OARSI) score (Assis, 2018). Other animal studies showed that PBMT was the most effective at reducing expression of genes for enzymes that degrade cartilage as compared to other treatment modalities (Tomazoni, 2016, 2017). A recent meta-analysis confirmed these findings, indicating a positive effect of PBMT, as indicated by lower cartilage defect in animal knee OA models (Xiang, 2020). One study with human participants found PBMT in combination with exercise therapy could increase IL-10 levels, however, it was limited to women and only assessed a few biomarkers in this disease cascade (Vasso, 2021). Therefore, more work is necessary in human knee OA populations to understand the biological cascade of PBMT.

Preliminary rat model research has indicated the complementing properties of the combination of PRP and PBMT in acute rheumatoid arthritis (Goncalves, 2021). This potential additive treatment approach offers an exciting opportunity to improve treatment interventions in this population. It, however, has not been applied in humans.

Given the relatively low risk of each of these treatments, and the debilitating nature of knee OA with the subsequent impact on military readiness, this potential pathway to management should be investigated, and the pathway by which this delay of degeneration occurs categorized with relevant biomarkers. This study will compare the effects of 1) standard PT treatment, and PT

plus, 2) PRP or 3) PBMT and PRP on the management of knee OA by using molecular medicine techniques to examine orthobiologics (synovial and serum inflammatory biomarkers) during the management process.

9.3 Objectives/Specific Aims/Research Questions:

Describe the purpose and objective(s) of the study, specific aims, and/or research questions /hypotheses

Aim 1: Use molecular medicine techniques to assess the effect of PBMT on intra-articular administered PRP for the treatment of knee osteoarthritis via evaluation of synovial and serum inflammatory and reparative biomarkers.

Aim 2: Use molecular medicine techniques to compare the results of Standard Care vs PRP vs PRP + PBMT in the treatment of knee osteoarthritis - using synovial and serum inflammatory and reparative biomarkers.

Aim 3: Analyze the relationship between self-reported pain and functionality and treatment mechanism (SOC, PRP or PRP +PBMT).

Aim 4: Analyze the intersectionality between participant self-reported pain and functionality and precision medicine markers across treatment groups (SOC, PRP, and PRP + PBMT)

9.4 Study Design:

Describe study design in one to two sentences (e.g., prospective, use of existing records/data /specimens, observational, cross-sectional, interventional, randomized, placebo-controlled, cohort, etc.). Specify the phase – Phase I, II, III, or IV – for FDA-regulated investigational drug research

This discovery-based and randomized control trial concerning knee OA will investigate the effect of PBMT and intra-articular administered PRP treatment on clinical outcomes (e.g., pain scores) and biomolecular signatures (DNA, RNA, or protein levels) in the blood or synovial spaces. We will specifically be comparing treatments, (1) PT, (2) PT+PRP, (3) PT+PBMT, (4) PT+PRP+PBMT, with clinical outcomes and biomolecular signatures.

9.5 Target Population:

Describe the population to whom the study findings will be generalized

Active-duty service members (ADSMs) and civilian populations experiencing knee OA

9.6 Benefit to the DoD:

State how this study will impact or be of benefit to the Department of Defense

Over 20,000 cases of knee OA were identified in the Active Forces over a span of ten years, and are rising in incidence. Current treatments for knee OA do not slow or halt the disease progression. The combination of PRP and PBMT has the possibility to enhance the management. This effective management could return ADSMs back to duty, ultimately increasing military readiness.

10.0 Study Procedures, Data Management, and Privacy

10.1 Study Procedures:

Describe step-by-step how the study will be conducted from beginning to end

Recruitment, Pre-Screening (before consent), Study Introduction & Informed Consent: About 1927 dependents and 1416 retirees with knee OA cases are seen by Madigan's Orthopaedic's department every year; 77 cases of knee pain and 135 patellofemoral OA were seen in the active-duty population. Thus, we should be able to recruit 150 participants in the next 2 years.

Potential participants will be identified via four methods:

1. Under the provisions of an approved Partial HIPAA Waiver Application for this study, local study team members will review medical records of patients coming in to the Sports Medicine, Physical Therapy, Orthopedic, Podiatry, and Physical Medicine & Rehabilitation (PM&R) clinics for suspected/confirmed knee OA in order to identify prospective research participants and to seek their authorization to participate/use their protected health information for this research study. The study team will receive approval from the potential participant's provider prior to approaching for possible study participation. As indicated in the Partial HIPAA Waiver Application for this study, the minimal amount of PHI necessary to screen for participants includes:
    - Names
    - Dates (except year) directly related to an individual (such as birth date, date of clinic visits, etc.)
    - DoD ID number
    - Relevant medical history (current and/or previous diagnoses and/or symptoms reported for the knee and associated treatments)
2. Direct referral from local healthcare providers in the local Sports Medicine, Family Medicine, Orthopedic and Podiatry, Physical Therapy, Holistic Health and Fitness (H2F), and Physical Medicine & Rehabilitation (PM&R) clinics.
3. Patients may self-refer to participate in the study. Interested potential participants will be able to contact a member of the study team via phone or email. Potential participants who contact the study team directly will be instructed to seek care with Orthopaedics, Sports Medicine, PM&R, or their primary care manager for a physical exam for a diagnosis of knee OA, if they do not already have a diagnosis.
4. Study advertisements will be posted within the following locations, and copies will be provided to clinic staff:
    - Internal Medicine
    - Aviation Medicine
    - H2F
    - McChord Clinic
    - Winder Clinic
    - Okubo Soldier-Centered Medical Home
    - Allen Soldier-Centered Medical Home
    - Soldier Recovery Unit
    - Puyallup Community Medical Home
    - South Sound Community Medical Home
    - Armed Forces Wellness Center
    - Intrepid Spirit Center
    - Madigan Medical Mall
    - Pharmacy waiting areas, if possible
    - Physical Therapy
    - Podiatry
    - Sports Medicine
    - Tactical Human Optimization, Rapid Rehabilitation and Reconditioning (THOR3)
    - Physical Medicine and Rehabilitation
    - Coffee bar
    - Dining Facility entrance
    - Intranet screen saver page
    - 2/75 Ranger Clinic

If a potential participant expresses interest in learning more about the research study, a member of the research staff will briefly introduce the study, express the voluntary nature of participation, assess interest in participating, and screen the potential participant for eligibility. Eligibility will be determined in person using the Inclusion/Exclusion Case Report Form (CRF) (Appendix A). Additionally, the potential participant may be provided with a study flyer (Appendix M).

Pre-screening conversations may also take place over the phone, should a participant contact the study team, using the Screening Script (Appendix N). Potential participants who meet initial eligibility per the Screening Script and express interest in participating will be asked to come to clinic to complete an Inclusion/Exclusion CRF (Appendix A) to confirm final eligibility with an

authorized study team member prior to providing informed consent as outlined in the respective section below.

If the potential participant meets eligibility criteria as determined by the Inclusion/Exclusion CRF and expresses interest in participating, an authorized study team member will initiate the formal consent discussion and, if applicable, obtain informed consent.

If a potential participant would like additional time to review the consent form, study procedures, risks and benefits, etc. they will be provided with a consent form to take home and, if applicable, they may return to clinic at a later date to have any and all remaining questions answered and to finish the consent process.

Following screening completion, the results of the Inclusion/Exclusion CRF will be entered into REDCap, an encrypted, access controlled, password protected electronic data capture and management system housed on a DoD server and maintained by the Uniformed Services University Information Technology (USU IT), and a unique study ID will be generated.

For participants who consented to participate, an excel document matching the participants unique study ID with their name and DoD ID will be stored in a password-protected electronic document on a CAC-enabled server; only on-site study team members will have access to this file. This coded study ID will be used on all research data collection forms in place of the participant's name, social security number, Department of Defense (DoD) ID, or other protected identifier. No PHI/PII will be entered into REDCap. Please see Appendix R for additional information on REDCap.

The research team will also keep a separate password-protected electronic screening log containing DoD ID number, eligibility/ineligibility status, and date screened will be kept by the research team in a secure folder on a secure drive, accessible only by authorized users. This log is needed to avoid any duplicative screening of those that are screen failures. This log, therefore, will include DoD ID numbers for those that screened formally and informally (by reviewing clinic schedule and records). This reduces burden on potential participants, providers, and study team and ensures the study team will not screen the same person twice or examine records for eligibility criteria when screen status is already established.

Contact Information Data Collection (post-consent):
Immediately following consent, the participant will complete an Intake CRF (Appendix B). The Intake CRF will collect participant contact information (full name, DoD ID number, preferred phone number, email address, etc.).

With the exception of the Consent Form and HIPAA Authorization, the Intake CRF is the only paper research form that will contain participant identifying information. It will be stored with the signed consent forms (in a locked cabinet inside of a locked room) and separately from all other paper research forms. All remaining paper research forms will be identified using a unique study ID and not by participant name, social security number, DoD ID, or other similar identifier. The Intake CRF will not be entered into REDCap (data storage system described more below).

Formal Screening, Demographics, & Baseline Data Collection:

Formal Screening (post-consent):
As part of the formal screening procedures, all consented participants that are biological females of child-bearing age and capacity will be required to complete a urine hCG pregnancy test, which will be ordered via EMR by a study provider, to confirm eligibility for study participation. MAMC Department of Pathology and Area Laboratory Services (DPALS) will complete urine sample collection and analysis and upload results in the participant's EMR. If the pregnancy test is positive, per the inclusion/exclusion criteria, the participant will be formally withdrawn from the study at this point, and will be encouraged to seek care with their primary care physician. If the pregnancy test is negative, the participant will be eligible to continue with the study procedures. The results of the pregnancy test will be entered into the EMR.

As part of the formal screening procedures, consented participants' final eligibility status will be confirmed via weightbearing knee X-rays, including AP, Rosenberg (45 deg knee flexion with beam from Posterior to anterior), and lateral views. If imaging was completed within one month prior to study enrollment, the previous images may be utilized. If diagnostic images are required, imaging will be ordered by an authorized medical provider. The results of the diagnostic images will determine if the participant meets final eligibility criteria (Kellgren-Lawrence grade 2 or higher, which demonstrates possible narrowing of the joint space with definite osteophyte formation), and should continue with the study intervention. A study physician will order X-Rays,

including AP, Rosenberg (45 deg knee flexion with beam from Posterior to anterior), and lateral views, or knee OA diagnosis. We will remove all personal identifying information from the images and only associate the images with the participant's assigned participant ID. These images will be stored securing within the TeleRay data platform. Please see Sections 10.14-10.15 for more information regarding Teleray.

Formal screening and confirmation of final eligibility status will be completed prior to study randomization.

Demographics & Baseline Data Collection:
Prior to receiving their assigned study treatment, participants will complete a Demographics CRF (Appendix C) and a Baseline Data Collection CRF (Appendix D). These questionnaires collect relevant data including: personal demography, military and employment demography, injury demography, and medical history, Fitzpatrick Skin Phototype, and validated self-reports.

A blood draw and a knee joint aspiration for synovial fluid will be conducted at baseline to assess for orthobiologics related to knee OA management (A complete list can be found in Section 10.2). Blood and synovial fluid date collection will be documented on the Baseline Data Collection CRF (Appendix D).

Blood Collection:
All team members will be trained, specifically in the methods of blood collection, safety, laboratory requirements, and processing, appropriate for their role in this study. These individuals will complete all training required by the MAMC lab, which can include hazardous materials handling, and biohazard safety.

The specimen collected in this study will not be used for clinical purposes.

An adequate amount of peripheral blood (approximately 11 ml) will be drawn by an experienced phlebotomist on the research team following standard sterile techniques. Blood will be collected into the appropriate blood collection tubes:

1. K2/EDTA Blood Tube 1 at 4ml
2. Heparin Blood Tube 1 at 4ml
3. DNA/RNA Shield Blood Collection Tube 1 at 3ml

The blood sample will be labeled with a sample ID (different from the study ID) and study visit, and transported to MAMC Department of Clinic Investigation (DCI) for storage and processing. Any excess blood sample will be safely discarded per standard protocol. Ice will be utilized for transportation, when necessary.

The blood samples will be processed by the DCI staff as described in the "Sample Processing" section below.

Synovial Fluid Collection:
Synovial fluid will be collected by the study team, including Orthopedic Surgeons, Physician Assistants, and Physicians at 3 possible locations:

1. MAMC Orthopedic Clinic
2. MAMC Sports Medicine Clinic
3. MAMC Physical Medicine and Rehabilitation

Synovial fluid will be aspirated according to standard of care (SOC) guidelines. If, at the time of joint aspiration, there is a "dry tap" (i.e., no fluid is returned), the provider will lavage the joint with a standardized quantity (10ml) of sterile Normal Saline and then aspirate the lavage. There are no harmful effects from lavaging the synovial joint with sterile saline.

The synovial fluid will be labeled with a sample ID and study visit, and transported to MAMC Department of Clinic Investigation (DCI) for storage and processing. Any excess synovial fluid will be safely discarded per standard protocol. Ice will be utilized when necessary.

Synovial fluid processing and storage are outlined below in respective sections.

The research team will maintain a biospecimen sample master key that links the sample IDs to the participant study IDs. No PII/PHI will be stored with the biospecimen sample key.

Randomization:
Participants that meet final eligibility criteria will be randomized to a study arm using a computer-generated randomization model prepared by the study biostatistician, to assign participant 1:1:1:1 across all study arms (PT, PT+PRP, PT+PBMT, or PT+PRP+PBMT).

Study Intervention:
Study interventions will be documented in the participant's EMR and on the Study Treatment Documentation Log (Appendix F).

Standard of Care (SOC) Physical Therapy (PT):
All participants will complete a standard PT program addressing individual strength, mobility, and flexibility deficits in both proximal and distal muscle groups. The provider may also use other modalities to address distal issues. If a participant has not been placed on profile at the time of consent, a profile may be written by the study medical provider to ensure limitation of activities, as appropriate.

The PT treatment participants receive in this study will be standard of care; that is, the PT treatment regimen will not be standardized across study participants and/or dictated by study-specific criteria. PT treatments will be recorded on a Chart Review CRF (Appendix I).

SOC PT + Platelet-Rich Plasma (PRP):
In addition to SOC PT, participants assigned to PT+PRP group will receive PRP treatment, as outlined below.

PRP Preparation:
The PRP will be prepared following standard technique by drawing 60cc blood from the participant through venipuncture, and spinning the blood sample in a centrifuge (for approximately 17 minutes), adjusting for leukocyte poor-platelet rich plasma (LP-PRP). This sample will be prepared by the study provider (physician assistant or physician). Any leftover blood will be safely discarded per standard protocols.

A small portion of the injectant PRP (approximately 1 cc) will be sent to MAMC DPALS for complete blood count (CBC) cytology to monitor standardization and reproducibility. This portion will be labeled by participant ID and study. De-identified hardcopy results will be obtained from MAMC DPALS, and CBC results will be reported on Appendix G (CBC Results CRF).

PRP Injection:
PRP injection procedures will follow current clinical recommendation and standard operating procedures. Prior to the injection, the area will be sterilely prepared and anesthetized with either ethyl chloride spray or lidocaine (limited to the cutaneous and subcutaneous layer, so as not to alter the synovial contents). Then, the participant will receive LP-PRP injection in the affected knee area under ultrasound guidance. Qualified study providers will inject 2-5cc LP-PRP using an 18-gauge 1/5-inch needle for both aspiration and subsequent injection. Study providers will select the injection portal they are most comfortable with, in order to achieve an accurate intra-articular injection. The PRP injection procedure is expected to take approximately one hour.

One PRP injection is sufficient to observing the necessary clinical and molecular medicine outcomes.

Post-procedural instructions will be provided in a participant handout (Appendix Q).

SOC PT + Photobiomodulation Treatment (PBMT):
In addition to SOC PT, the PBMT group will receive PBM treatment, as outlined below.

PBM treatments will occur 3 times each week, for 3 weeks. A member of the study team will measure the treatment area according to a standard protocol and calculate the treatment time (approximately 5-20 minutes). PBMT will be delivered at 6 J/cm2 and 25W and applied in a serpentine pattern to the knee area. Participants will be asked to refrain from using perfumes or plant extracts (e.g., St. John's Wort) in the treatment area(s), as this can increase skin photosensitivity.

The PBMT will be provided by a trained study team member. Training for the PBMT will be conducted by a LightForce representative. PBMT will be delivered using the LightForce® XPi 25W device with the Smart Hand Piece technology, created by LiteCure, LLC/DJO (New Castle, DE) which has a built-in accelerometer in the hand piece that controls the speed of light delivery to the treatment area. The LightForce® XPi therapy laser is an FDA cleared device for the treatment of pain. The trained team members will use the Smart Hand Piece technology, which achieves effective treatments and improves dosing accuracy by assessing the operator's speed and providing real-time visual (red – amber – green light) and sensory feedback. The Smart Hand Piece is calibrated to shut-off when moving too slowly, and warn the operator when moving too fast by vibrating. (See LightForce Brochure). The therapy is delivered through a flexible optical fiber threaded through the hand piece, which contains a rolling glass massage ball.

SOC PT + PRP + PBMT:
In addition to SOC PT, the PRP and PBMT group will receive PRP treatment (outlined above) and PBM treatment (outlined above).

Participants in this group will start PBM treatments on the same day after receiving the study PRP injection. On the day of the PRP injection, the participant will be instructed to rest for 5-10 minutes prior to the PBMT application and team member will ensure the participant is comfortable not in pain. Immediately following the study injection, the team member will take care not to provide the PBMT over the injected area; however, all subsequent PBM treatments will be delivered to the knee where the PRP was injected.

Concomitant Medications & Treatments:

Allowed Concomitant Medications:
Patients are allowed acetaminophen and usual medications.

Prohibited Treatments:
Participants will be asked to avoid NSAIDs/COX-2 inhibitors and ASAs for 5 days prior to and 2 weeks following their study injection or beginning of treatment.

Oral steroids, steroid injections, and viscos supplementation are not permitted for the study duration in the treated knee.

Follow-Up Data Collection:
Regardless of study arm assignment, all participants will be asked to log their activity, overall function rating, pain, and medication intake (Appendix E), daily, for 6 weeks. A team member will check-in with the participant weekly to collect the activity log.

A self-report battery will be obtained using Appendix H Follow-Up Data Collection CRF, which will be administered at 3-weeks and 6-weeks post-intervention start.

A follow-up blood draw and synovial fluid aspiration will be completed at 6 weeks. The blood and synovial fluid samples will be processed by MAMC DCI staff as described in the "Sample Processing" section below.

Additionally, a chart review will be completed at 6 weeks to ensure that all related medical visit information is recorded in study documentation (Appendix I). A medical record review will be completed to obtain this information. A study visit is not required on behalf of the participant.

Participants will be evaluated for adverse events at each follow-up time point and any complications will be documented.

Data may be captured in person or remotely (e.g., entered directly into REDCap using a personalized coded link with no log-in required, verbally over the phone with a study team member, etc.). Reminder phone calls, texts, and/or emails will be sent to participants at their preferred contact method indicated on the Intake Form (Appendix B).

The Study Completion CRF (Appendix J) will be completed by a study team member to document the completion or withdrawal of all study participants.

Please see the Study Flow Diagram (Appendix L) for a visual representation of the study procedures.

Missed Appointments and Study Removal:
If a participant misses a scheduled appointment, they will be contacted to reschedule in order to maintain the treatment plan of their assigned study treatment group. In the event that a participant misses an appointment, study staff will make one attempt to reschedule each day on three separate days (for three total attempts to reschedule). If the participant cannot be reached or does not respond/reschedule, they will be removed from the study due to non-compliance.

Specimen Storage and Analysis:
All specimens will be collected, processed, and analyzed according to the recommendations of the respective manufacturer, current laboratory SOPs, or software recommendations. *When possible,* study staff will be blinded to treatment groups.

Molecular analyses will be performed over the following 6 months but may go on longer depending on the scope of assays performed, e.g. orthogonal validation.

Specimen Storage
Samples stored at MAMC DCI will be coded using the Biospecimen Master Key (Appendix S) that links the sample IDs to the participant study IDs. The Biospecimen Master Key will be kept on a CAC-enabled, secure laptop.

MAMC DCI will maintain samples collected during the course of this protocol until they are exhausted. Tracking and storage of biological samples will be performed according to established SOPs with protocol specific modifications. MAMC DCI will maintain de-identified sample IDs and information regarding: samples processed/received, sample storage location/access/usage, quality control information (acquisition of correct sample; rapid sample preservation; timely transportation to the repository; routine and continuous monitoring). Study team members will visually inspect the samples for integrity and verify the date/time the samples were collected.

All specimens will be coded and specimen information will be stored electronically. The PI of this study will be the point of contact for the access and utilization of biological samples for experimental procedures.

Specimen Processing
These sample analyses will provide insight into the internal biological cascade/changes of protein expression over time, that may inform the effectiveness of treatment/management of knee OA with PRP and PRP + PBMT treatments.

We plan to quantify protein expression, and we may do so using protein panels (e.g., a Bio-Plex kit) or lower throughput methods (e.g., ELISA or Western blot), if necessary. We may also attempt to use flow cytometry. Substrate for protein expression analyses will be plasma, synovial fluid, or synovial fluid pellets.

Note: It is possible that that there could be an insufficient number of cells in the synovial fluid pellet to perform flow cytometry. In the future, if time and resources allow, we may also perform mass spectrometry, as our sample collection methods are compatible with mass spectrometry. At the moment, however, we have no immediate plans to use the technique. If we choose to pursue this technique in the future, we will consult with mass spectrometry experts.

We plan to quantify RNA expression, and we may do so using RNA panels (e.g., an nCounter panel), sequencing (e.g., on a MiSeq or MinION), or lower throughput methods (e.g., qPCR). We may also perform single cell sequencing (e.g., using synovial fluid pellets resuspended and frozen in phosphate buffered saline and dimethyl sulfoxide). MAMC DCI presently lacks the latter sequencing capability, so samples would need to be shipped. If we choose to pursue single cell sequencing at a later time we may need to send specimens to a vendor or collaborator for processing. We will not do so until all regulatory requirements have been met (e.g., a protocol modification, data sharing agreement, contract, etc.). We will consult with MAMC HRPO, IRB, and other DCI personnel to ensure these requirements are met. Substrate for RNA expression analyses will be blood in DNA/RNA Shield blood tubes and synovial fluid pellets. However, we may later use the other specimens (e.g., synovial fluid) which could contain miRNAs or other products of interest.

In regard to DNA analyses, we may screen for the presence of single nucleotide polymorphisms via amplicon sequencing. This will be done in a targeted fashion based on review of the literature. The raw data from these findings will neither be used to identify patients nor be published.

Gene expression levels will be quantified using techniques appropriate for the specific substrate. For example:

- DNA - Data will be generated in fastq format using a sequencing instrument (e.g., MiSeq, NextSeq, MinION) that may generate intermediate formats (e.g. bcl2, fast5) that require processing to arrive at the fastq format. Data may also be converted to SAM, BAM, VCF, BCF, or a similar format. Other data formats may be used if needed.
- RNA - Data will be generated in fastq format (if performing sequencing, e.g., with a MiSeq, NextSeq, MinION) and summarized as counts at the isoform or gene level. To arrive at the count level, raw data will be processed by performing alignment, pseudo-alignment, or any other mapping technique. Different software may be used to do this, e. g. Sleuth. Statistical analyses will be performed using standard workflows, e.g. DESeq2, edgeR. We may also use RNA quantification methods such as the nCounter, PCR arrays, and qPCR. For the latter methods, we will use the manufacturer's software (e.g. nSolver), the delta delta Ct method, or standard curves for absolute quantification. We will use loading controls such as GAPDH, RPLP0, or similar when needed.
- Protein - We will perform ELISAs (generate spectrophotometric data), Western blots (generate densitometric data), use arrays or multi-plex or other intermediate throughput techniques (e.g., Olink, BioPlex), mass spectrometry data (outputs vary but will be summarized into counts or relative expression levels), or other relevant methodologies.

Sample processing is as follows:

- *Synovial Fluid:*
  - Synovial fluid (SF) will be collected in a 1.5 mL Eppendorf tube (ept).
  - SF sample will be transferred to the lab on ice.
  - SF sample will be centrifuged at 1500g for 15 min in a refrigerated centrifuge to clear SF from cellular debris.
  - Supernatant (synovial fluid) will be immediately transferred into a clean 1.5 mL ept.
  - Protease inhibitor will be added at 1X final concentration (100-fold dilution of the original 100X).
  - 200-500µL of SF will be aliquoted into a pre-labeled 1.5 mL tube and stored at -80° C.

- *Proteomics analysis:*
  - *4-5 mL of blood will be collected into a sodium heparin tube, and an additional 4-5 mL of blood will be collected into a K2 EDTA tube.*
  - *Blood samples will be transferred to the lab within 20 minutes of collection.*
  - *Blood samples will be centrifuged at 2000 g for 15 minutes using a refrigerated centrifuge.*
  - *The top liquid component (plasma) will be immediately transferred into a clean 15 mL polypropylene conical tube.*
  - *Protease inhibitor will be added at 1X final concentration (100-fold dilution of the original 100X).*
  - *200-500 µL of plasma will be aliquoted into a pre-labeled 1.5 mL tube and stored at -80°C.*

- *DNA/RNA analysis:*
  - *3ml of blood will be drawn into a DNA/RNA Shield Blood Collection Tube.*
  - *Blood samples will immediately be inverted 10 times (gently).*
  - *Blood sample will be transported at 4°C to MAMC DCI.*
  - *Once at DCI, samples will be aliquoted into cryovials (200-500ul each) and stored at -80°C.*
  - *At a later date, when a complete batch of samples are available, samples meant for genomic or transcriptomic analyses will be thawed at 4°C or room temperature and their nucleic acids will be extracted using a kit appropriate for the sample and nucleic acid type (e.g., Zymobiomics Microbial DNA extraction kit or Qiagen DNA and RNA extraction kits).*
  - *Extracted DNA and RNA will be stored at -80°C for later processing.*
  - *DNA or RNA extracts will be barcoded using the appropriate protocol (e.g., for 16S or RNA sequencing on the Illumina MiSeq) and processed according to the manufacturer's protocols or as needed following experimental optimization.*

Once sufficient sampling has been met, batch analyses will be completed for the respective biomarkers of interest. Single sample analysis may also occur for optimization and preliminary results.

These assays will evaluate many matrix and immune markers that may include ADAMTS-4 & 5, MMP 7 & 9, TGF-B, Aggrecan, HYAL2, CRP, HA, CD14, CD16, and CD64.

Additional Info - MIRROR/USU:
This research study is being conducted as part of Musculoskeletal Injury Rehabilitation Research for Operational Readiness (MIRROR), which is based out of the Department of Physical Medicine & Rehabilitation (PM&R) at the Uniformed Services University (USU).

MIRROR is focused on advancing musculoskeletal injury (MSI) rehabilitative care within the military healthcare system in order to reduce the burden MSIs have on military readiness and to ultimately enhance the operational capabilities of the armed forces. MSIs affect approximately 800,000 service members annually and result in 25 million days of limited duty. These conditions are the primary reasons for medical discharge/downgrade and result in 34% of medical evacuations from theatre. MIRROR was developed as a means to study risk factors of common MSIs, generate prevention strategies, optimize treatments, and establish return-to-duty criteria that is based on scientific evidence rather than case-specific clinical judgment alone.

MIRROR involves interdisciplinary and inter-service partnerships, the Department of Defense (DoD), and several major academic medical centers. To ensure military mission focus and scientific relevance, MIRROR is guided by a steering committee composed of members from the Joint Program Committees (JPCs) at the U.S. Army Medical Research and Development Command (USAMRDC), military operational leaders, and experts in musculoskeletal medicine from the military and civilian communities. MIRROR aims to be the world's leader in military relevant musculoskeletal injury care research.

Currently, research projects are being deployed at more than 20 military and civilian treatment facilities nationwide.

MIRROR/USU is serving as a Coordinating Center for this study and will also be providing remote regulatory support. Staff from MIRROR/USU will not interact with human subjects and will not have access to the paper research records or any identifiable research data to include the Master List, the Informed Consent Documents/HIPAA Authorizations, or any other form of participant PHI /PII. Deidentified research data will shared with MIRROR/USU and maintained indefinitely for possible use in future research.

If applicable, appropriate data sharing agreements will be in place.

10.2 Data Collection:

Describe all the data variables, information to be collected, the source of the data, and how the data will be operationally measured.

Please see attached Data Collection Schedule (Appendix K).

The local study team will obtain the information necessary to complete the study Case Report Forms (CRFs) (see Appendices A-J) from several sources including the participant's medical record (i.e., relevant medical and treatment history and relevant clinical notes), clinical evaluations, from their attending provider(s), and directly from the participant (including in person, via mail or email, or over the phone).

With the exception of the Intake CRF (Appendix B) which collects contact information, all paper CRFs will be identified using a unique study ID only, and not by the participant's name, social security number, DoD ID, or other protected identifier.

Questionnaires:

- The Demographics CRF (Appendix C) and the Baseline Data Collection CRF (Appendix D) will be used to will be used to obtain demographic/military/medical information and Fitzpatrick Skin Phototype (rating of susceptibility to skin damage from ultraviolet (UV) radiation).
- Defense and Veteran's Pain Rating Scale (DVPRS) basic will capture pain daily.
- Single Assessment Numeric Evaluation (SANE) will capture function daily.
- Activity and medication use will also be recorded in a self-report diary.

- Knee Injury and Osteoarthritis Outcome Score (KOOS) will capture knee symptoms and associated functional status at baseline, 3 weeks, and 6 weeks post-intervention.
- The Veterans Rand 12 Item Health Survey (VR-12) will capture overall functional and health status at baseline, 3 weeks, and 6 weeks post-intervention.

PRP CBC analysis results will be reported on Appendix G (CBC Results CRF).

A chart review will be conducted at the end of 6 weeks to capture all SOC/PT visits.

We will use protein expression quantification and genetic analysis to target specific biomarkers in the areas of inflammatory mediators, growth factors, and intra-articular, structural homeostasis mediators.

10.3 At any point in the study, will you request, use, or access health information in any form, including verbal, hard copy and electronic?

(•) Yes ( ) No

10.4 Review the definitions below and respond to the following two questions. If you are not sure of the answers, email DHA.PrivacyBoard@mail.mil for assistance. The *Military Health System (MHS)* is defined as all DoD health plans and DoD health care providers that are organized under the management authority of, or in the case of covered individual providers, assigned to or employed by, the Defense Health Agency (DHA), the Army, the Navy, or the Air Force *MHS workforce members* are employees, volunteers, trainees, and other persons whose conduct, in the performance of work for the MHS, is under the direct control of the MHS, whether or not they are paid by the MHS. *MHS business associates* are persons or entities that provide a service to the MHS and require protected health information (PHI) to provide the service.

Are you an MHS workforce member?

(•) Yes, I am an MHS workforce member
( ) No, I am not an MHS workforce member

Are you an MHS business associate?

( ) Yes, I am an MHS business associate
(•) No, I am not an MHS business associate

10.5 Have you consulted with an MHS data expert to determine the data elements required for your study?

Consulting with a data expert often saves time later in the compliance process because the data expert can advise on the data available in the numerous MHS information systems, the quality of that data and the methods for encrypting and collapsing data. To schedule a consult with an MHS data expert, send an email to: (**DHA.PrivacyBoard@mail.mil**)

( ) Yes, then complete the questions below according to the data consult
(•) No, then complete the questions below according to the best of your knowledge

10.6 Indicate how you will request data from the MHS. Select all that apply.

[x] Talking with MHS health care providers or MHS health plans about specific research participants
[ ] Obtaining MHS hard copy records specific to research participants
[x] Obtaining data from an MHS information system(s)

10.7 If you are obtaining data from an MHS information system(s), indicate whether you plan to receive a data extract or whether you plan to access an MHS information system directly to create a data set.

A data extract is when the MHS or a contractor provides the data set directly to the researcher. When receiving a data set through data extract, the researcher may indicate whether the data elements should be provided as is, encrypted or collapsed. In contrast to a data extract, access to an information system means that the researcher may directly access an MHS information system and create a data set for the research study

- [ ] Data Extract
- [x] Access

10.8 Do you intend to request de-identified data from the MHS in your research study?

There are different two methods for de-identifying data pursuant to HIPAA:
1) Safe Harbor Method: Removing all of the identifiers listed in Table 1 below, provided that the researcher does not have actual knowledge that the remaining data can be used alone or in combination with other information to identify the individual who is the subject of the information
2) Statistical Method: An expert, with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable, determines that the data is not individually identifiable

- ( ) Yes
- (•) No

10.9 Indicate the MHS information system(s) from which you will seek to obtain data

If you do not know which system(s) contains the data elements you need, refer to the Guide for DoD Researchers on Using MHS Data or request guidance from an MHS data expert at: **DHA.PrivacyBoard@mail.mil**.

Below is a list of commonly used MHS systems. If the system from which you seek to obtain data is not listed below, list the name of the system in the "Other MHS Systems" category below
PHI Systems:

MHS Information System	Requesting Data
: CHCS	: Yes

PII-Only Systems:

MHS Information System	Requesting Data
No records have been added	

De-Identified Data & Other Systems:

Information System	Requesting Data
Other MHS System (May include PII and/or PHI) List other system here: Genesis	: Yes

10.10 Do you intend to merge or otherwise associate the requested data with data from any sources outside of the MHS, including other DoD systems that are not part of the MHS?

- ( ) Yes, will merge data
- (•) No, will not merge data

10.11 Indicate the data elements about research participants or relatives, employers, or household members of the research participants that you will request from MHS hard copies or from MHS

information systems.
If you will merge data, also indicate non-MHS data elements about research participants or relatives, employers, or household members of the research participants that you will have access to in any form or medium.

Direct and Indirect Identifiable Data Elements	DHA Hard Copies	DHA Data Elements to be Accessed	DHA Data Elements Verbal	Extracted DHA Digital Data	Downloaded DHA Digital Data	Non-DHA Hard Copies or Digital
1. Names	☐	☑	☐	☐	☐	☐
2. Postal address with only town, city, state, and zip code	☐	☐	☐	☐	☐	☐
3. Postal address with all geographic subdivisions smaller than state, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of Census: 1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and 2) the initial three digits of a zip code from all such geographic units containing 20,000 or fewer people is changed to 000	☐	☑	☐	☐	☐	☐

4. Dates including all elements (except year) directly related to an individual, including birthdate, admission date, discharge date, and date of death	☐	☑	☐	☐	☐	☐
5. Ages over 89 and all elements of dates (including year) indicative of such age, unless you will only request a single category of "age 90 or older"	☐	☐	☐	☐	☐	☐
6. Telephone Numbers	☐	☑	☐	☐	☐	☐
7. Fax Numbers	☐	☐	☐	☐	☐	☐
8. Email Addresses	☐	☑	☐	☐	☐	☐
9. Social Security Numbers	☐	☐	☐	☐	☐	☐
10. Medical Record Numbers (MRN) (including record ID)	☐	☐	☐	☐	☐	☐
11. Health Plan Beneficiary Numbers (including DEERS ID, Electronic Data Interchange	☐	☐	☐	☐	☐	☐

Personal Identifier (EDIPI) or Number (EDIPN))						
12. Account Numbers	☐	☐	☐	☐	☐	☐
13. Certificate /License Numbers	☐	☐	☐	☐	☐	☐
14. Vehicle identifiers and serial numbers, including license plate numbers	☐	☐	☐	☐	☐	☐
15. Device identifiers and serial numbers	☐	☐	☐	☐	☐	☐
16. Web Universal Resource Locators (URLs)	☐	☐	☐	☐	☐	☐
17. Internet Protocol (IP) address numbers	☐	☐	☐	☐	☐	☐
18. Biometric identifiers, including finger and voice prints	☐	☐	☐	☐	☐	☐
19. Full-face photographic images and any comparable images	☐	☐	☐	☐	☐	☐
20. Any other unique identifying number, characteristic, or code	☐	☑	☐	☐	☐	☐

(including non-military provider IDs)						
21. Free Text Fields	☐	☐	☐	☐	☐	☐

If you are obtaining SSNs, provide a justification as to why and explain why a substitute cannot be used.

Due to guidelines stated within DoDI 1000.30, Reduction of SSN Use within DoD, the reduction or elimination of SSN usage must occur wherever possible. If SSNs are required to complete the project, the PI must provide a justification and explanation as to why a substitution cannot be used.
For example:

- If alternatives to SSN (e.g., EDIPNs or pseudo person IDs) are sufficient in other instances, will those alternatives to SSN usage be sufficient to respond to Congressional inquiries and /or Senior DoD stakeholders inquiries?
- Are alternatives to SSN used first?
- Are those alternatives to SSN insufficient to combine data from multiple data sources? Is the issue that some individuals do not possess alternatives ID numbers and SSN is the only way to identify them?

N/A

a. Will you receive or obtain health information?

> ***Note:*** *If you indicate you are not receiving health information, the answer must be consistent with the DHA data source. For a non-health information data request, if you are a non-MHS employee or non-MHS business associate, you may not access an information system that has PHI or LDS. For both MHS and Non-MHS employees and MHS business associates, you may* ***NOT*** *include data elements in the above table on: 1) lines 10 or 11, 2) line 21 if the free text field comes from a PHI or LDS system, and 3) lines 12, 13, or 18 if the account numbers, certificate and license numbers, biometric data, or any other data elements are health information created or received by an MHS health care provider, health plan, or business associate in relation to the physical or mental health or condition of an individual or payment for health care.*

◉ Yes, I will receive or obtain health information
○ No, I will not receive or obtain health information

b. If no data elements were checked in the above table, is it possible that the requested DHA data is or will be identifiable because of any unique data elements, triangulation, or small cell size?

☑ Data elements were checked in the above table, STOP HERE.

NOTE: *A unique data element includes any unique features that alone are not identifiable but that could be used to identify an individual within the context of other information, such as any type of code (such as diagnosis or procedural), rank of general or admiral, gender, or race. Triangulation means using different data elements that when combined can be used to identify an individual, such as including the above lists of unique data elements in a data set. Determining whether an individual is identifiable through triangulation requires consideration of all data elements in combination. Within the military, the use of rank and/or diagnosis code, procedural codes, or any other code that changes on a predictable basis, increases the possibility of identification. Small cell size means that there is only a small number of eligible individuals that satisfy the category description. Department of Defense Manual 6025.13, Medical Quality Assurance and Clinical Quality Management in the Military Health System MHS, provides that the threshold for de-identifying data within the MHS requires a cell size of three, but also states that the de-identification standards must meet the DoD implementation of the HIPAA Privacy Rule. Centers for Medicare and Medicaid also gives guidance on small cell size stating that no data cell*

less than 11 may be published or displayed. However, the Office for Civil Rights' OCR, which is the official regulatory office for the HIPAA Privacy Rule, provides that OCR does not designate a universal value for small cell size in accordance with the de-identification standard; instead, the cell size should be set at a level that is appropriate to mitigate risk of identification by the anticipated recipient of the data set. This means that a cell size of 3 or 11 may not meet the HIPAA Privacy Rule requirements if the cell size level does not appropriately mitigate risk of identification by the anticipated recipient of the data set.

Note: If dates are altered as a means of de-identifying the data, diagnosis and procedural codes need to be rolled-up or collapsed. If dates are provided "as time between events," the roll-up is not necessary.

- ☐ Yes, the DHA data will become identifiable
- ☐ No, the DHA data will not become identifiable

10.12 Do you believe it is possible for the MHS data to become identifiable because of triangulation, a small cell size, or any unique data element(s)?

Triangulation means using different data elements that are not themselves identifiable but that when combined can be used to identify an individual. For example, triangulation would use rank and race together to determine the identity of an individual with a particular health condition.

Small cell size means that there is only a small number of eligible individuals that satisfy the category description. Guidance for acceptable cell size is available from the Centers for Medicare and Medicaid Services. For example, the rank category of four star generals with a particular diagnosis may be less than 30, so the rank category may need to be expanded to include lower ranks.

A unique data element includes any unique features that are not explicitly enumerated in the categories of data in rows 1 – 20 of the table above (in Section 10.10), but that could be used to identify an individual. Unique data elements include characteristics that are not themselves identifying, such as the rank of general or admiral, or a race or gender, but within the context of other information could be identifiable.

- ○ Yes, I believe there is a reasonable possibility the MHS data will become identifiable
- ◉ No, I believe there is no reasonable possibility the MHS data will become identifiable

10.13 Have you completed and uploaded an appropriate HIPAA document (i.e. HIPAA Authorization will be obtained or Waiver/alteration of HIPAA Authorization is being requested)?

- ◉ Yes
- ○ No
- ○ N/A

If yes, please check which one.

- ○ HIPAA Authorization
- ○ HIPAA Waiver (Full or Partial)
- ◉ Other (please provide copies when uploading Other Study Documents)

10.14 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for this Study:

Include in this section the plan for acquiring data (both electronic and hard copy), access during the study, data/specimen storage and length of time stored, shipment/transmission, and the plan for storage and final disposition at the conclusion of the study. Describe any data agreements in place for accessing data within and/or outside of your institution (e.g., Data Sharing Agreement, Data Use Agreement, Business Agreements, etc.)

Specimen Acquisition, Access, and Storage
Specimens will be sampled following consent as described in detail in section 10.1.

During study conduct, only study personnel will have access to the study specimens. The specimens will be stored in freezers at MAMC DCI. Specimens will be stored without identifying information on their labels; a unique sample ID generated for this study will be used to label specimens. A biospecimen sample key will be maintained to link sample IDs with participant study IDs.

Data Capture Methods:
The local study team will collect study data directly from the study participant (including in person, via mail or email, or over the phone), from their attending provider(s), clinical evaluations or, where applicable, from the participant's medical record (i.e., relevant medical and treatment history and relevant clinical notes) and record it on study Case Report Forms (CRFs). (See Appendices A-J).

The completed CRFs will serve as source documents for this study. Other source documents include relevant clinical notes, imaging, and/or test results which, if applicable, will be redacted and stored in the participant's research file.

Participants may also enter their coded data directly into REDCap using a personalized survey link (no log-in required). In these cases, the personalized survey link will be provided to the participant by a study team member (i.e., participant email addresses will not be entered into REDCap, and REDCap will not autogenerate emails directly to study participants). The completed REDCap questionnaire(s) will be printed and added to the participant's research record as a source document.

Electronic Data Entry:
Following each research visit, a local study team member will review any completed paper CRFs for accuracy and completeness and then enter the collected non-personally identifiable data from the paper CRFs into REDCap, an encrypted, access controlled, password protected electronic data capture and management system housed on a Department of Defense (DoD) server and maintained by the Uniformed Services University Information Technology (USU IT).

Please see Appendix R for additional information on REDCap.

X-ray images will also be uploaded to TeleRay (more information is outlined below).

Data Storage & Access:
With the exception of the Informed Consent Form, HIPAA Authorization, Intake CRF, and electronic Master List, all research data (both paper and electronic) will be identified using a unique study ID only, and not by the participant's name, date of birth, DoD ID, or other protected identifier.

Paper research forms and source documents will be stored in a locked cabinet inside of the designated research office in the Orthopaedics Clinic.

Coded x-ray images will be uploaded to TeleRay. Teleray ensures that all accounts stored in Microsoft Azure's self-healing network with advance security protocols enabled and is only located in the USA Secure Connection: The sessions established are secure (with secured tokens that are regenerated). Random AES keys are generated by clients at the beginning of the media connection and, to increase security, additional keys are generated periodically throughout the session. TeleRay employs Transport Layer Security (TLS) to encrypt video data. The core protocols used are Secure Real-time Transport Protocol (SRTP) for media traffic encryption and Datagram Transport Layer Security (DTLS)-SRTP for key negotiation, both of which are defined by the Internet Engineering Task Force (IETF). The endpoints use Advanced Encryption Standard (AES) cipher with 256-bit keys to encrypt audio and video, and Hash-based Message Authentication Code- Secure Hash Algorithm 1 (HMAC-SHA1) to verify data integrity. No PHI/PII will be entered into TeleRay. Access to the coded data uploaded to TeleRay will be controlled and managed by the local MAMC research team.

The coded electronic research data for this study will be stored in REDCap, an encrypted, access controlled, password protected electronic data capture and management system housed on a Department of Defense (DoD) server and maintained by the Uniformed Services University Information Technology (USU IT). No PHI/PII will be entered into REDCap.

This coded electronic research data will be accessible by authorized staff from Musculoskeletal Injury Rehabilitation Research for Operational Readiness (MIRROR) which is based out of the Department of Physical Medicine & Rehabilitation (PM&R) at the Uniformed Services University

(USU) and is serving as the data coordinating center for this research study. Access to the electronic coded research data will be governed strictly on an individual-by-individual basis within REDCap. Individual data access as well as privileges will be clearly delegated, audited, and monitored by MIRROR/USU. Staff from MIRROR/USU will not have access to the paper research records or any identifiable research data.

The local study team will maintain a separate electronic master list which matches unique study IDs with participant identifying information. The electronic master list will be stored separately from the coded electronic research data in a secure, password protected document on a computer and network that requires CAC access and will only be accessible by local research staff.

All research data and forms (both paper and electronic) will only be accessible by authorized study staff, authorized staff from MIRROR/USU (coded data entered into REDCap and Teleray only, as described above), the IRB of record, the local research office (if applicable), and applicable governmental agencies as part of their duties and in accordance with federal law. These duties include making sure that research participants are protected.

If applicable, appropriate data sharing agreements will be in place.

Informed Consent Forms and HIPAA Authorizations will be maintained for a period of 6 years following study closure and then securely shredded. Paper research forms will be maintained for a period of 5 years following study closure and then securely shredded. The master list connecting unique study ID to participant identifiers will be destroyed as soon as all data collection is completed and analyzed, and no later than one year following study closure. The electronic coded research data will be maintained indefinitely as described below in protocol section 10.15. The PI will be responsible for ensuring the destruction schedule is adhered to.

Is this a data repository?

○ Yes ◉ No

If Yes, provide name of the Repository.

Who will have access to the Repository?

What data type will be stored in the Repository?

☐ PHI
☐ LDS
☐ De-identified Data

10.15 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for Future Research:

If the study involves collecting, storing, or banking human specimens, data, or documents (either by the Investigator or through an established repository) for FUTURE research, address. How the specimens/data will be used, where and how data/specimens will be stored (including shipping procedures, storage plan, etc.), whether and how consent will be obtained, procedures that will fulfill subjects' request as stated in the consent, whether subjects may withdraw their data/specimens from storage, whether and how subjects may be recontacted for future research and given the option to decline, whether there will be genetic testing on the specimens, who will have access to the data/specimens, and the linkage, the length of time that data/specimens will be stored and conditions under which data/specimens will be destroyed.

Consent for Future Use of Data:
The Informed Consent Form for this research study states that de-identified research data will be shared with MIRROR/USU and maintained indefinitely for possible use in future research. By consenting to participate in this research study, participants agree to allow us to maintain their de-identified research data indefinitely for possible use in future research.

Participants will not be given the option to opt out of us retaining their de-identified research data indefinitely for possible future use. The consent form states, "If you do not want your de-identified data collected as part of this research study to be kept for use in future research studies, you should not sign this consent form."

Consent for Future Use of Specimens:
The Informed Consent Form for this research study states that de-identified biospecimens will be maintained indefinitely for possible use in future research. By consenting to participate in this research study, participants agree to allow us to maintain their de-identified biospecimens indefinitely for possible use in future research.

Participants will not be given the option to opt out of us retaining their de-identified biospecimens indefinitely for possible future use. The consent form states, "If you do not want your de-identified biospecimens collected as part of this research study to be kept for use in future research studies, you should not sign this consent form."

Participants will be given the opportunity to consent to future use of their coded (identifiable) specimens at the same time they consent to participation in the study. Any future research will require appropriate regulatory reviews and approvals. If a participant opts to allow the study team to maintain their identifiable biospecimen, their identifiable information from the study master list will also be maintained after study closure.

A study team member will transcribe the participants' election from the ICF to opt in/out of future use of identifiable biospecimens in the Master List (Appendix P). This information will also be recorded on the Biospecimen Master Key (Appendix S).

Long Term Specimen Storage
Retained study samples (de-identified for all participants or coded for those who opt in) will be stored long term in the MAMC Department of Clinical Investigation. Only authorized personnel will have access to these specimens. Specimens will be stored without identifying information on their labels. A unique sample ID generated for this study will be used to label specimens. This will be the only link between the specimen and the participant study ID. Specimens will be stored until they have been used up or until it is no longer feasible to maintain them. When appropriate, specimens will be destroyed in accordance with the laboratory's safety protocols. The PI will be responsible for ensuring their destruction by DCI staff.

All participants that opt in to use of identifiable biospecimens for future studies will be transferred to a new "master list" at study closure. All original master list data elements will be retained. Participants that do not opt in to use of identifiable biospecimens for future studies will not be transferred to the new "master list." The original master list will be destroyed at study closure. The original biospecimen master key will be maintained indefinitely.

Long Term Data Storage & Access:
The de-identified electronic dataset will be maintained by MIRROR/USU and the study team indefinitely or as long as it is practicable to maintain.

The de-identified data uploaded to TeleRay will be maintained by the local research team indefinitely, or as long as it is practical to maintain, and while funding is allotted for this service.

De-identified electronic research data will be securely transmitted from local study teams to the MIRROR /USU via REDCap, Teleray, or the DoD SAFE application (or other comparable safe data sharing system implemented by the local site and/or the US Army/DHA). REDCap utilizes Secure Sockets Layer (SSL) in addition to other safeguards on its web server to maintain secure communication with end-users (see Appendix R). DoD SAFE uses a TLS (Transport Layer Security) protocol when files are uploaded and downloaded. TeleRay employs Transport Layer Security (TLS) to encrypt video data. The core protocols used are SRTP for media traffic encryption and DTLS-SRTP for key negotiation, both of which are defined by the IETF. The endpoints use AES cipher with 256-bit keys to encrypt audio and video, and HMAC-SHA1 to verify data integrity.

Once received, the electronic de-identified research data will be stored within an encrypted, access controlled, password protected electronic data capture and management system housed on a Department of Defense (DoD)-compliant server.

Access to the de-identified research data will be governed strictly on an individual-by-individual basis within the secure electronic data capture and management system. Individual data access as well as privileges will be clearly delegated, audited, and monitored by MIRROR/USU. Any future research using retained data will require a research protocol to be approved by an Institutional Review Board or other authorized official responsible for protecting human subjects of research.

Any future research using retained data will require a research protocol to be approved by an Institutional Review Board or other authorized official responsible for protecting human subjects of research.

Data/Specimens Withdrawal from Storage:
Participants may request to have their data/specimens withdrawn at any time before their personal identifiers have been removed. Once their data has been de-identified, it will be impossible for the researchers to locate their specific study data.

Is this a data repository?

(•) Yes ( ) No

If Yes, provide the name of the Repository

(1) USU OCIO REDCap (2) Teleray (3) Photomedicine & PRP Treatment Biorepository

Who will have access to the Repository?

(1) USU OCIO REDCap - De-identified data only: Study investigators, study team members, and MIRROR Core team members, as appropriate. Access to the de-identified research data will be governed strictly on an individual-by-individual basis within the secure electronic data capture and management system. Individual data access as well as privileges will be clearly delegated, audited, and monitored by MIRROR/USU.

(2) Teleray - De-identified data only: Study investigators, study team members, and MIRROR Core team members, as appropriate. Access to the de-identified research data will be maintained /delegated by the local research team on an individual-by-individual basis.

(3) Photomedicine & PRP Treatment Biorepository - De-identified and coded biospecimen- Study investigators, study team members, and MIRROR Core team members, as appropriate. Access to either the de-identified biospecimen or coded biospecimen will be maintained/delegated by the local research team as directed by the study investigator, on an individual-by-individual basis.

What data type will be stored in the Repository?

- [ ] PHI
- [ ] LDS
- [x] De-identified Data

11.0 Statistical/Data Analysis Plan

11.1 Statistical Considerations:

List the statistical methods to be used to address the primary and secondary objectives, specific aims, and/or research hypotheses. Explain how missing data and outliers will be handled in the analysis. The analysis plan should be consistent with the study objectives. Include any sub-group analyses (e.g., gender or age group). Specify statistical methods and variables for each analysis. Describe how confounding variables will be controlled in the data analysis

This is an interventional and discovery-based protocol that will identify associations between molecular and demographic information and clinical outcomes.

Descriptive statistics will report location and scale in terms of mean and standard deviation for normally distributed variables, median and interquartile intervals for ordinal metric variables, and in terms of proportion and size for categorical variables. Descriptive statistics will be reported for baseline demographic and clinical characteristics at an overall level and by initial treatment group.

Outliers will be removed if determined to be erroneous based on relevant clinical expertise. Confounding will be principally controlled by randomization. In regards to the treatment of

missing data, subjects with missing baseline or 6-week follow-up data will be excluded from Aim 1 analyses regarding change from baseline to six weeks but will be included in Aim 2 analyses across all relevant time points.

Statistical methods
For categorical variables, statistical methods may include tests such as the Fisher's exact test, Chi-square test, McNemar's test, or binomial test. For ordinal variables that do not approximate a continuous variable, tests such as ordinal logistic regression will be performed. For ranked data, tests such as Friedman's test will be used. For continuous random variables (ratio or interval types) or ordinal data that approximates a continuous random variable (e.g., Likert scale), t-tests will be used. The Wilcoxon signed rank test or Wilcoxon rank sum test will be used if the assumptions for the t-test do not hold. The normality assumption may be evaluated with a test that is appropriate given the sample size, objective, and intended audience, e.g., Shapiro-Wilk test, Jarque-Bera test, Kolmogorov-Smirnov test, or Anderson-Darling test. For analyses with more than two groups in the single independent variable or for analyses with more than one independent variable, single or multi-way ANOVAs will be performed, respectively. If a continuous variable is a potential covariate, then an ANCOVA will be performed. Post hoc tests will include tests such as Tukey's, Dunn's, Dunnett's, or pairwise univariate tests with false discovery rate correction, depending on the objectives of the analysis. Sequencing data will be analyzed using techniques that include negative binomial regression, PERMANOVA, and ANOSIM. Clustering will be performed using techniques such as hierarchical, k-means, k-medoids, Gaussian mixture models. These methods will attempt to minimize (or maximize depending on the metric) an error metric such as silhouette score, Akaike Information Criterion, or Bayesian Information Criterion with the specific metric being selected based on the best practice in the field, e.g., silhouette score for k-means. Clustering may be performed with or without first performing dimensionality reduction using Principal Components Analysis, Non-metric Multi-Dimensional Scaling, t-SNE, U-MAP, or another similar technique, depending on the data types, number of variables, and objectives. When analytic methods are unavailable, bootstrapping may be performed to estimate uncertainties, e.g. confidence intervals. Alternatively, if Bayesian methods are applied, then credible intervals will be calculated. When decision trees and decision-tree based methods (e.g., random forest, decision jungles) are used, feature importance may be calculated. When developing predictive models, both simple, explainable models (e.g., linear and logistic regressions) will be used when possible. When incorporating larger numbers of variables, neural network based models may be used. When such methods are applied, the optimum number of layers, dropout, activation functions, nodes, and other elements of model architecture will be determined empirically. Data will be split into training, cross validation, and testing groups in accordance with best practices in the machine learning and artificial intelligence fields. Regarding correlation analyses, correlations will be identified via methods that include Pearson's, Spearman's, and Kendal's tau. The specific method will be selected based on the bivariate distribution of the data, e.g. monotonic and linear vs. monotonic but not linear. Hoefding's D statistic may be calculated for non-monotonic relationships.

Missing data
Missing data will be handled as required by the statistical methods used:

1. For most analyses this means excluding the observations for which a relevant value is missing.
2. For some analyses, such as decision trees, missing values will be grouped together to create a new category.

Outliers
Outliers will be handled using a method appropriate for the statistical method used. For example, they may be excluded for parametric methods, however, they may be included when using non-parametric methods. If a non-parametric method cannot be used (e.g., none exist or they are not sufficiently interpretable), then the outlier may be excluded or replaced with a more appropriate value (e.g., a randomly selected value, the median, or one determined via an imputation method such as Multiple Imputation by Chained Equations). Results with and without the outlier will be compared to determine whether its exclusion impacts conclusions.

Sub-group analyses
Sub-group analyses will be performed for variables for which there is existing evidence (e.g., in the literature) or reason to suspect that they differ between groups. Such analyses may be performed as separate analyses (e.g., one analyses per group) or via incorporation of the grouping variable into the statistical model as in linear or logistic regression.

Handling confounding variables
When possible, confounding variables will be incorporated into models to control for their effects, e.g., in logistic regression. Whether confounders are included exclusively as direct effects or as direct effects plus interaction terms depends on the clinical nature of the variable. The most appropriate method of inclusion will be determined via discussions between medical staff and a statistician and/or bioinformatics analyst.

11.2 Sample Size:

Assuming attrition and accounting for screen failures, we are requesting to enroll up to 200 (50 per arm) participants in order to evaluate a final sample of 92 (30-31 per arm).

11.3 Total number of subjects requested (including records and specimens):

200

11.4 If you are recruiting by study arm, please identify the arms of the study and how many subjects will be enrolled in each arm

Up to 200 participants will be randomized 1:1:1:1 to the four treatment arms.

11.5 Please provide a justification for your sample size

Since this is a discovery-based study of a novel topic, limited data are available with which to perform a power analysis. Thus we used a G*Power for a general comparison analysis without needing to root firmly in one specific variable.

If we are able to enroll 150 participants (a minimum of 92 post-attrition), assuming an effect size of .2, we will achieve 90% power. Effect size assumptions were taken from Tomazoni et al. 2016 based on the comparison of control versus PBMT with regards to biomarkers of gene expression that we assume to be an acceptable proxy for our primary comparison with regards to our biomarkers of concern. Significance threshold for power calculations was considered to be . 01 to account for false discovery rate within our set of primary biomarker outcomes. Power calculations were performed using the WebPower package and the R Programming language.

11.6 Data Analysis Plan: Complete description: Background, Objectives, Design, Step by Step how the project is going to be done, Data analysis plan:

Aim 1 will be evaluated by comparing the PRP only and the PRP + PBMT treatment arms at six weeks relative to baseline. Generalized additive models predicting the fractional change in outcome measure at 6 weeks will be used.

Aim 2 will compare across all four treatment arms and will use Multi-Level models comparing the three treatment arms across time points and including random effects.

Aim 1 will include biomarker measures only; Secondary Aim 2 will include both biomarker measures and self-reports.

Hypothesis tests will be two-tailed and statistical significance will be considered at the putative threshold (alpha=0.05). Any secondary P-values will be subject to a false discovery rate adjustment in keeping with best statistical practices. Multilevel models will incorporate random effects to account for repeated measures, using distribution families and link functions appropriate for the outcomes of interest, determined using QQ plots analyzed for best model fit. All statistical analyses will be performed using the R Programming language.

Clinical outcomes (pain scores) will be evaluated via ANOVA and post-hoc tests (Tukey's HSD test). A non-parametric alternative will be used if assumptions are not met.

Molecular Analyses:

DNA/RNA Analyses
DNA/RNA analyses will be performed using the software Galaxy or Geneious or any similar software packages such as Bioconductor for the R programming language. Specific statistical methods will depend on the variables of interest, but will include Fisher's exact test or Chi-square test for categorical data, logistic or linear regression for dependent variables with binary and continuous outcomes, respectively, and PCA, t-SNE, or U-MAP for dimensionality reduction, the first step in unsupervised clustering. The unsupervised clustering techniques that follow will include those listed above for microbiome profiling but may also include techniques better suited to specifically Cartesian coordinate data such as k-means. The latter would be accomplished following projection of the data into a Cartesian plane, e.g. via non-metric multidimensional scaling (NMDS). Data collected via the nCounter platform, qPCR data, or any data collected using a similar technology will be analyzed in accordance with the manufacturer's recommendations (e. g., t-test, linear regression, etc.). Sequence alignment for the purpose of biomarker identification (e.g., SNP detection) will be performed using Bowtie2 or similar software as standalone command line based software or via a graphic user interface (GUI) embedded within Galaxy, Geneious, or another package. Differential expression analysis for transcriptomic data will be performed using standard tools and workflows (e.g., Salmon, Kallisto, Sleuth, DESEQ2, edgeR, Coordinate Covariation Analysis, epigenomix, etc.).

Proteomic Analyses
Maximum-likelihood techniques based on the negative binomial distribution will be used to model proteomics count data and Wald statistics, two-tailed t-test, analysis will be utilized to analyze the primary and secondary outcomes. Any missing data that cannot be obtained via chart review or interview of the caring provider will be omitted and documented as such. In some case where the confounding variables cannot be eliminated or minimized through experimental design, the confounding variables will be included in the analysis to control for their effects. Data analysis will be conducted using both standalone proteome discoverer with Sequest, Mascot search engine and R-programming languages established for high throughput proteomics data analysis here in DCI. For orthogonal validation data sets will be analyzed with the various statistical algorithms that are established in DCI.

Correlation Analyses
Associations between clinical, demographic, and gene expression, genetic, and microbial data will be identified by calculating correlations and other metrics of associations. For example, Pearson's correlation will be used to detect presumptive linear associations. Spearman's correlation or Kendal's tau will be used to detect non-linear but still monotonic relationships. Hoeffding's D statistic will be used to detect more complex, possibly non-monotonic, relationships. Multivariate approaches (e.g., linear or logistic regressions) will be used to control for potential covariates.

Predictive Analytics
We will model return to duty time rate and time using a combination of analytic methods that enable prediction and inference. First, we will use methods such as logistic regression and decision trees to support inference about the factors that contribute the most to returning to duty. Second, we will use methods such as multivariate regression, support vector machines, and neural networks to predict the rate of and time to return to duty. The latter approach will enable the integration of a broader array of variables than the former methods. The overall result will be inclusion of not only pre-operative and post-operative outcome variables but also biomolecular signatures.

12.0 Participant Information

12.1 Subject Population:

DEERS eligible adults (age 18-64, inclusive) diagnosed with knee OA

12.2 Age Range:

Check all the boxes that apply. if the age range of potential subjects (specimens, records) does not match the range(s) selected, please specify in the text box.

- ☐ 0-17
- ☑ 18-24
- ☑ 25-34

- [x] 35-44
- [x] 45-54
- [x] 55-64
- [ ] 65-74
- [ ] 75+

12.3 Gender:

- [x] Male
- [x] Female
- [ ] Other

12.4 Special categories, check all that apply

- [ ] Minors /Children
- [ ] Students
- [x] Employees - Civilian
- [ ] Employees - Contractor
- [ ] Resident/trainee
- [ ] Cadets /Midshipmen
- [x] Active Duty Military Personnel
- [ ] Wounded Warriors
- [ ] Economically Disadvantaged Persons
- [ ] Educationally Disadvantaged Persons
- [ ] Physically Challenged (Physical challenges include visual and/or auditory impairment)
- [ ] Persons with Impaired Decisional Capacity
- [ ] Prisoners
- [ ] Pregnant Women, Fetuses, and Neonates
- [ ] Non-English Speakers
- [ ] International Research involving Foreign Nationals - Headquarters Review is necessary

You must also consider the requirements of DoDI 3216.02, paragraph 7.e.

You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e.

12.5 Inclusion Criteria:

Order Number	Criteria
1	DEERS eligible
2	Between the ages of 18-64 (inclusive) years
3	Meets the American College of Rheumatology (ACR) diagnostic criteria for knee osteoarthritis-- i.e., Knee pain AND at least three of the following criteria: 1. >50 years old 2. Morning stiffness <30 minutes 3. Crepitus on active movements 4. Tenderness of the bony margins of the joint 5. Bony enlargement 6. No palpable warmth Ability to read and understand English language for consent purposes

4	
5	Ability to commit to study intervention and follow-up
6	Willingneess to avoid prohibited treatments while enrolled in the study (i.e.,_ NSAIDs/COX-2 inhibitors and ASAs for 5 days prior to and 2 weeks following their study injection or beginning of treatment, and Oral steroids, steroid injections, and viscos supplementation are not permitted for the study duration in the treated knee).
7	Radiographic evidence of knee osteoarthritis as assessed by Kellgren-Lawrence grade 2 or higher (may be assessed during formal screening, post-consent)

12.6 Exclusion Criteria:

Order Number	Criteria
1	Current participation in other research studies for knee OA
2	Previous enrollment for contralateral knee
3	Hx of arthroscopic surgery on the study knee within the past year
4	Hx of arthroplasty on the study knee
5	Received dry needling within the past 4 weeks
6	Received prolotherapy (e.g., CSI or PRP injection), within past month
7	Recent (within the last 3 months) lower extremity injury (e.g., ankle sprain, meniscus tear or sprain, etc.) that required professional medical attention, and occurred in the ipsilateral extremity of the study knee
8	Confounding, coexisting pathology suspected to be the primary source of their pain [e.g., acute meniscal tear (with mechanical symptoms), ligamentous changes (with clinical instability) or hemarthrosis]
9	Current or chronic sciatica (lumbosacral radiculopathy) resulting in chronic or intermittent lower extremity pain, numbness, or tingling
10	Diagnosis of neuropathy affecting sensation to pain
11	Diagnosis of inflammatory arthropathy
12	Diagnosis of fibromyalgia or chronic fatigue syndrome
13	Hx of adverse reaction to a PRP injection (either documented in the medical record or shared by the patient during screening)
14	Tattoo in treatment area
15	Diagnosis of porphyria (light induced allergy) or photosensitive eczema
16	Current use of medications associated with sensitivity to heat or light (e.g., amiodarone, chlorpromazine, doxycycline, hydrochlorothiazide, nalidixic acid, naproxen, piroxicam, tetracycline, thioridazine, voriconazole)
	Current use of pacemaker

17	
18	Hx of underlying cardiac disease
19	Diagnosis of autoimmune disease
20	Albinism
21	Current pregnancy or plans to become pregnant during intervention period
22	Hx of memory problems, dementia, and/ or impaired decision-making ability
23	Any other serious medical condition(s) that might preclude optimal outcome and /or interfere with participation (e.g., intra-articular sepsis, bacteremia, fracture, joint instability, rheumatoid arthritis, osteoporosis, cancer, coagulopathy, etc.)

13.0 Recruitment and Consent

13.1 Please describe the recruitment process, including how subjects will be identified and selected for the study.

Please see Study Procedures Section 10.1

Potential participants will be identified via four methods:

1. Under the provisions of an approved Partial HIPAA Waiver Application for this study, local study team members will review medical records of patients coming in to the Sports Medicine, Physical Therapy, Orthopedic, Podiatry, and Physical Medicine & Rehabilitation (PM&R) clinics for suspected/confirmed knee OA in order to identify prospective research participants and to seek their authorization to participate/use their protected health information for this research study. The study team will receive approval from the potential participant's provider prior to approaching for possible study participation.
2. Direct referral from local healthcare providers in the local Sports Medicine, Family Medicine, Orthopedic and Podiatry, Physical Therapy, Holistic Health and Fitness (H2F), and Physical Medicine & Rehabilitation (PM&R) clinics.
3. Patients may self-refer to participate in the study. Interested potential participants will be able to contact a member of the study team via phone or email. Potential participants who contact the study team directly will be instructed to seek care with Orthopaedics, Sports Medicine, PM&R, or their primary care manager for a physical exam for a diagnosis of knee OA, if they do not already have a diagnosis.
4. Study advertisements will be posted within the following locations, and copies will be provided to clinic staff:
    - Internal Medicine
    - Aviation Medicine
    - H2F
    - McChord Clinic
    - Winder Clinic
    - Okubo Soldier-Centered Medical Home
    - Allen Soldier-Centered Medical Home
    - Soldier Recovery Unit
    - Puyallup Community Medical Home
    - South Sound Community Medical Home
    - Armed Forces Wellness Center
    - Intrepid Spirit Center
    - Madigan Medical Mall
    - Pharmacy waiting areas, if possible
    - Physical Therapy
    - Podiatry
    - Sports Medicine
    - Tactical Human Optimization, Rapid Rehabilitation and Reconditioning (THOR3)
    - Physical Medicine and Rehabilitation
    - Coffee bar

- Dining Facility entrance
- Intranet screen saver page
- 2/75 Ranger Clinic

The local research team will keep a separate electronic screening log containing DoD ID number, ineligible/eligible, and date screened. This log will be password protected and stored in a secure folder on a secure drive accessible only by authorized local research staff. This log is needed to avoid any duplicative screening of those that are screen failures. This reduces burden on potential participants, providers, and study team and ensures the study team will not screen the same person twice or examine records for eligibility criteria when screen status is already established.

Recruitment and consent conversations will take place in a private setting (e.g., closed clinic room, investigator's office, etc.) to minimize the potential opportunity to be overheard or inadvertently witnessed.

13.2 Compensation for Participation:

Participants may receive up to $150 for their participation in this research.

There are three opportunities to receive compensation:

(1) when a participant completes the baseline blood draw - $50,
(2) when a participant turns in the completed daily activity log at the 3-week follow-up visit - $50, and
(3) when a participant completes the 6-week follow-up blood draw - $50.

Participants will receive payment in the form of a gift card or Visa-type card equivalent.

Participants will only be paid for applicable research activities that they complete. They will not receive compensation for research activities they do not complete.

In accordance with the DoDI 3216.02, all human subjects (including federal employees both on and off-duty) participating in DoD-conducted or supported research may be compensated up to $50 for each blood draw. Additionally, DHA-AI 3200.01 indicates active-duty service members may receive additional compensation for the completion of a daily health diary when completed off-duty. In accordance with DHA-AI 3200.01 the following definitions of on-duty and off-duty will apply to active duty-service member study participants:

- An individual is on-duty when they are expected or required to perform the duties of their assigned job or position.
- An individual is off-duty if the individual is not scheduled to perform any work that may arise during the period.

In order to receive compensation for the completion of the daily activity log in this research, a study team member will ask the participant to confirm that they completed the daily activity log while off-duty/on leave. It will be the responsibility of the study participant to provide accurate information regarding their duty/leave status at the appropriate compensation interval.

Upon request, the PI and/or authorized study team member may provide certification for intermittent leave, or leave on a reduced leave schedule, for planned study medical treatment(s) (in accordance with US Code Title 5, Section 6383).

13.3 Please describe the pre-screening process. If no pre-screening, enter Not Applicable in the text editor

This study has two screening phases: 1) Pre-screening based on initial inclusion/exclusion criteria (before informed consent) and 2) a formal screening phase to determine eligibility for randomization to intervention arm (after informed consent).

Pre-Screening (before consent):
If a potential participant expresses interest in learning more about the research study, a member of the research staff will briefly introduce the study, express the voluntary nature of

participation, assess interest in participating, and screen the potential participant for initial eligibility in close collaboration with the patient's attending provider. Pre-screening conversations may also take place over the phone using the Screening Script (Appendix N).

Initial eligibility (see Protocol Sections 12.5 *Inclusion Criteria* & 12.6 *Exclusion Criteria*) will be confirmed in-person using an Inclusion/Exclusion CRF (Appendix A). This Inclusion/Exclusion CRF does not record any PII/PHI.

Individuals that do not meet inclusion/exclusion criteria will be encouraged to continue to seek care with their primary care provider.

If the potential participant meets eligibility criteria as determined by the Inclusion/Exclusion CRF and expresses interest in participating in the study, an authorized study team member will initiate the formal consent discussion and, if applicable, obtain informed consent. See protocol section 13.4 for additional information on the consent process.

Formal Screening (post-consent):
As part of the formal screening procedures, all consented participants that are biological females of child-bearing age and capacity will be required to complete a urine hCG pregnancy test. If the pregnancy test is positive, per the inclusion/exclusion criteria, the participant will be formally withdrawn from the study at this point, and will be encouraged to seek care with their primary care physician. If the pregnancy test is negative, the participant will be eligible to be randomized to a study arm and continue with the study procedures.

As part of the formal screening procedures, consented participants' final eligibility status will be confirmed via X-ray. If imaging was completed within one month prior to study enrollment, the previous images may be utilized. If diagnostic images are required, imaging will be ordered by an authorized medical provider. The results of the diagnostic images will determine if the participant meets final eligibility criteria (Kellgren-Lawrence grade 2 or higher, which demonstrates possible narrowing of the joint space with definite osteophyte formation), and should continue with the study intervention.

13.4 Consent Process: Revised Common Rule, Section 219.116: General requirements for informed consent, whether written or oral, are set forth in this paragraph and apply to consent obtained in accordance with the requirements set forth in paragraphs (b) through (d) of this section. Broad consent may be obtained in lieu of informed consent obtained in accordance with paragraphs (b) and (c) of this section only with respect to the storage, maintenance, and secondary research uses of identifiable private information and identifiable biospecimens.

Are you requesting a waiver or alteration of informed consent?

○ Yes ◉ No

Please explain the consent process:

Consent will be obtained in accordance with principles of Belmont Report and Common Rule guidelines.

The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the signed consent form will be given to the participant and the original will be stored in a locked cabinet inside of a locked office. Documentation of consent will be recorded in the participant's medical record. No Legally Authorized Representatives will be utilized.

Formal consent, as represented by the act of signing a dated, IRB approved consent statement for the study will only occur after confirming eligibility using the Inclusion/Exclusion CRF, a thorough review of what is involved in the study, and after all questions have been answered.

Potential participants will be provided information regarding all available study treatments and reminded of the expectations placed on them if they enroll, including the randomization process.

The potential participant will be given a copy of the informed consent document to read before, during, and/or after discussion of the informed consent with the Research Coordinator (RC), Principal Investigator (PI), Associate Investigator (AI), or other authorized study team member. Sufficient time will be given to the potential participant to understand the study purpose, study procedures, time commitments, potential risks and benefits, and the types of health information

that will be accessed, collected, and used by the research team if they agree to participate in the study.

Questions can be raised by the potential participant at any time during the consent discussion and at any time during the conduct of the study. The potential participant will be instructed that their participation is completely voluntary and that they may withdraw from the study at any time without penalty. Their decision to participate or to not participate, or to withdraw from the study after consent, will not affect their access to health care that they are otherwise entitled to and it will not affect their military position.

The authorized study team member present during the consent conversation will confirm that the potential participant has no additional questions before deciding to provide consent.

Every effort will be made to eliminate the perception of authority, which is a particularly important consideration when recruiting active-duty study participants. When applicable, the study investigators will be in scrubs or civilian clothes instead of uniform and will introduce themselves as doctor rather than their military rank. Some potential participants may be patients of the study PI or AI. In these cases, the consent conversation will be initiated by non-physician study staff to prevent any misconception of coercion or undue influence.

Informed consent and HIPAA authorization will be obtained in person.

In the event that there are significant new findings regarding the therapy that may affect participants' willingness to continue in the study, an information sheet will be provided to all current and past participants. The informed consent document will be amended for future participants.

Following completion of informed consent, the results of the Inclusion/Exclusion CRF will be entered into REDCap, an encrypted, access controlled, password protected electronic data capture and management system housed on a DoD server and maintained by the Uniformed Services University Information Technology (USU IT), and a unique study ID will be generated. This coded study ID will be used on all research data collection forms in place of the participant's name, Department of Defense (DoD) ID, or other protected identifier. No PII will be entered into REDCap.

Please see Appendix R for additional information on REDCap.

13.5 DoDI 3216.02 requires an ombudsman to be present during recruitment briefings when research involves greater than minimal risk and recruitment of Service members occurs in a group setting. If applicable, you may nominate an individual to serve as the ombudsman.

- (•) N/A
- ( ) Propose ombudsman

13.6 Withdrawal from Study Participation:

Explain the process for withdrawal and specify whether or not the subjects will be given the opportunity to withdraw their data their data/specimens in the event they wish to withdraw from the study

Participant Withdrawal:
Participants may withdraw from the study at any time without penalty. Participants will be informed that withdrawal will not affect their access to health care that they are otherwise entitled to and it will not affect their military position.

If a participant withdraws from the study, we may retain and analyze all coded/de-identified data collected up to the time of withdrawal if the data is necessary to maintain the integrity of the study. However, no further data will be collected after the date of withdrawal.

Participants may contact the study research coordinator/assistant or Principal Investigator to formally withdraw from the study. Participants will be advised to follow-up with their personal physician if they choose to withdraw.

Withdrawal Without Participant Consent:

A participant may be withdrawn from the study without their consent if remaining in the study might be dangerous or harmful to them. Participation may also be stopped if the military mission requires it, if they lose their right to receive medical care at a military hospital, if the study is canceled, if they fail to adhere to the protocol and/or therapy plan, or if they display inappropriate behavior towards study personnel.

14.0 Risks and Benefits

14.1 Risks of Harm:

Identify all research-related risks of harm to which the subject will be exposed for each research procedure or intervention as a result of participation in this study. Consider the risks of breach of confidentiality, psychological, legal, social, and economic risks as well as physical risks. Do not describe risks from standard care procedures; only describe risks from procedures done for research purposes

Diagnostic Imaging:
Knee X-rays will be completed in this study as part of the formal screening procedures. If imaging was completed within one month prior to study enrollment, the previous images may be utilized. There is no known minimal level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects (cellular abnormalities) or cancer. However, the risk associated with the amount of radiation exposure received from this study is considered to be extremely low when compared to the everyday risks.

Blood Draw/Venipuncture and Joint Aspirations
There are also common but minor risks associated with blood draws and joint aspirations. These potential risks include: discomfort, bruising, hematoma, redness, swelling, light-headedness, fainting, nerve damage and, rarely, infection.

Physical Therapy (PT)
Possible risks associated with physical therapy treatment include: worsening of pre-existing conditions, continued and/or increased pain that may limit activities, no improvement in mobility or strength, soreness, or failing during and/or injury from physical therapy exercises and/or performance-based tests.

Platelet-Rich Plasma (PRP)
Risks of the PRP injection include donor site/administration site pain, bleeding, infection, damage to surrounding neurovascular structures, hypersensitive or allergic reaction, venous thrombosis, skin discoloration, inefficacy, and need for further procedures.

Photobiomodulation (PBM) Therapy
The risks associated with PBMT are minimal. PBMT is used by a variety of healthcare practitioners for painful clinical conditions. Mild discomfort may be experienced during the treatment, the treatment should not be "hot", but participants should notify the study team member if they feel any uncomfortable warming. Individuals with neuropathies or difficulty distinguishing changes in skin temperature are at higher risk. Potential research-related risks include damage to eye structures, headaches post-procedure, uncomfortable skin heating or erythema/redness, which are both very rare.

Additionally, any time information is collected for a study, there is a small risk of breach of confidentiality.

14.2 Measures to Minimize Risks of Harm (Precautions, safeguards):

For each research procedure or intervention, describe all measures to minimize and/or eliminate risk of harms to subjects and study personnel

All available measures to minimize risks will be taken in accordance with standard clinic protocols.

The risks associated with diagnostic imaging, ultrasound, and blood draw procedures will be mitigated by using trained professionals that follow industry standards for minimizing these risks.

The laser device will be processed through MAMC Property and safety checked through Healthcare Technology Management and Sustainment (HTMS) before being used. A member of the research team will serve as a clinical laser safety officer (CLSO) to establish and manage the study-specific laser safety program. The designee will work with the MAMC Laser Safety Officer (LSO) and participate in the MAMC Laser Safety Committee (LSC) meetings quarterly to receive proper training. Along with the LSO and CLSO, the PI will ensure that the treatment space meets all regulatory requirements for utilization of a treatment laser, including appropriate signage and use of laser blocking screens to absorb any potential scatter/refraction of light outside of the treatment area.

All applicable study team members will complete a battery of training modules and hands-on training sessions to ensure safe operation of the PBMT device, and compliance with local laser safety requirements and American National Standards Institute (ANSI) standards Z136.1 (Safe Use of Lasers) and Z136.3 (Safe Use Lasers in Health Care). See Appendix T for the laser operator training plan.

Protective eyewear will be worn by all participants and study team members during PBMT treatment sessions to avoid potential eye damage. In the rare occurrence that participants experience uncomfortable warmth over the treatment area during PBMT, the treatment will be modified or stopped.

In order to reduce the risks associated with the injection procedures, the team will ensure proper verification of allergies, standard injection site preparation, sterile instrument use, and standard sterile procedure. Venipuncture and aspirations will be conducted by trained personnel.

In order to protect participant confidentiality, research data will be identified using a unique study ID only, and not by participant name, date of birth, DoD ID, or other similar identifier. Biospecimen will be identified be a separate unique sample ID, and not by any direct identifiers. All available measures allowed by law will be taken by research staff to protect participant confidentiality. See protocol section 14.3 for additional information.

All participants will be evaluated for adverse events at each follow-up visit. All adverse events, regardless of severity, will be reported to the Principal Investigator. Adverse events will also be reported according to the guidelines stated in Protocol Section 16.

14.3 Confidentiality Protections (for research records, data and/or specimens):

Describe in detail the plan to maintain confidentiality of the research data, specimens, and records throughout the study and at its conclusion (e.g., destruction, long term storage, or banking). Explain the plan for securing the data (e.g., use of passwords, encryption, secure servers, firewalls, and other appropriate methods). If data will be shared electronically with other team members/collaborators outside the institution, describe the method of transmission and safeguards to maintain confidentiality. Explain whether this study may collect information that State or Federal law requires to be reported to other officials or ethically requires action, e. g., child or spouse abuse

Upon consenting for the study, participants will be assigned a unique study ID. With the exception of the Informed Consent Form with embedded HIPAA Authorization, and electronic Master List, all research data (both paper and electronic) will be identified using this unique study ID only, and not by the participant's name, date of birth, DoD ID, or other protected identifier.

Paper research forms and source documents will be stored in a locked cabinet inside of a locked room, accessible only by local research staff designated and authorized by the Principal

Investigator. The paper Intake CRF which records participant contact information, Informed Consent Forms with embedded HIPAA Authorizations will be stored separately from the coded paper research forms in a locked cabinet inside of a locked room, accessible only by authorized local research staff.

The coded electronic research data for this study will be stored in REDCap, an encrypted, access controlled, password protected electronic data capture and management system housed on a Department of Defense (DoD) server and maintained by the Uniformed Services University Information Technology (USU IT). The local study team will manage the storage and upload of ultrasound in TeleRay, which is an encrypted and access controlled data platform. No PHI/PII will be entered into REDCap or Teleray. See Appendix R for additional information on REDCap.

The local study team will maintain a separate electronic master List which matches the unique study IDs with participant identifying information. The electronic Master List will be stored separately from the coded electronic research data in a secure, password-protected electronic document, on a government computer and network that requires CAC access, and will never be printed.

At the time of biospecimen collection, participants will be assigned a unique sample ID. A separate biospecimen master key, which matches the biospecimen sample ID to the participant study ID, will not contain any direct identifying information. The electronic biospecimen master key will be stored separately from the study master list and coded electronic research data in a secure, password-protected electronic document on a computer and network that requires CAC access.

All research data and forms (both paper and electronic) will only be accessible by authorized study staff, the IRB of record, the local research office, and applicable governmental agencies as part of their duties and in accordance with federal law (except as stated in the next paragraph). These duties include making sure that research participants are protected.

Musculoskeletal Injury Rehabilitation Research for Operational Readiness (MIRROR), which is based out of the Department of Physical Medicine & Rehabilitation (PM&R) at the Uniformed Services University (USU), is serving as the data coordinating center for this research study. As such, authorized staff from MIRROR/USU will have access to the coded research data that is entered into REDCap. Authorized staff from MIRROR/USU will not have access to the electronic Master List, the paper research records, or any participant PHI/PII.

There will be appropriate data sharing agreements in place.

Any research data shared with an approved agency for review will be linked only to the participant's unique study ID and not with the personal identity of the participant (i.e., name, DOB, DoD ID, address, phone number, etc.). If the research data is used in scholarly presentations or journal articles, the investigators will protect the anonymity of individual participants and report only aggregate data (e.g., group means) where appropriate.

Participants will not be individually identified in any publication or presentation of research results.

14.4
Potential Benefits:

Describe any real and potential benefits of the research to the subject and any potential benefits to a specific community or society

If the individuals in the research are considered experimental subjects (per 10 USC 980), and they cannot provide their own consent, the protocol must describe the intent to directly benefit all subjects

We cannot guarantee that participants will benefit from participation in this research study. The aim of this study is to improve recovery of knee osteoarthritis (KOA), it is expected that all treatment arms will help KOA, some treatments potentially quicker than other more traditional treatment options.

14.5
Privacy for Subjects:

Describe the measures to protect subject's privacy during recruitment, the consent process, and all research activities, etc.

Recruitment, consent conversations, and follow-up research activities will take place in a private setting (e.g., closed clinic room, investigator's office, etc.) to minimize the potential opportunity to be overheard or inadvertently witnessed. Information being collected will be limited to only the minimum amount of data necessary to accomplish the proposed research.

No uniformed service members or supervisors will be present during recruitment and consent discussions.

14.6
Incidental or Unexpected Findings:

Describe the plan to address incidental findings and unexpected findings about individuals from screening to the end of the subject's participation in the research. In cases where the subject could possibly benefit medically or otherwise from the information, state whether or not the results of screening, research participation, research tests, etc., will be shared with subjects or their primary care provider. State whether the researcher is obligated or mandated to report results to appropriate military or civilian authorities and explain the potential impact on the subject

There is the possibility incidental findings could reveal information the participant would not otherwise be aware of. In cases where the participant could possibly benefit medically or otherwise, the participant will be notified and, when appropriate, so will their primary care provider. Research representatives will not share incidental and unexpected findings with anyone else unless required by law.

In cases involving military personnel, information regarding their health may be required to be reported to appropriate medical or command authorities to ensure the proper execution of the military mission, including evaluation of fitness for duty.

Although unlikely, incidental findings could impact a participant's future ability to receive health or life insurance, as is the case with all medical care. Incidental findings may also make the participant feel anxious.

Incidental Findings:
Participants will not have the option to decline receiving incidental findings in this study. The PI will review all incidental findings and determine whether or not the incidental finding should be reported to the participant. The PI will utilize guidance provided by OHRP *Attachment F - Recommendations on Reporting Incidental Finding.* Specifically, the PI will consider whether the findings are validated and actionable, and if they have potential implications for a participants physical and mental wellbeing. The PI will assume responsibility for notifying participants of incidental findings, explaining the findings, implications, and recommendations for next-steps to follow-up with their clinical care team.

Incidental Findings of *Future Studies*:
A study team member will transcribe the participants' election from the ICF to opt in/out of receiving results of incidental findings from future research studies in the Master List (Appendix P). This information will also be recorded on the Biospecimen Master Key (Appendix S).

If a participant elects to receive incidental findings of future research studies and they agreed to storage of their identifiable biological specimens, then the principal investigator of the respective research study will be responsible for notifying the participant as indicated by procedures in their study-specific protocol.

If a participant elects to receive incidental findings of future research studies and they did not agree to storage of their identifiable biological specimens, then incidental findings may only be

relayed to the study participant while this protocol is open and the original master list exists. Once the original master list is destroyed, the participant's biospecimens will be completely de-identified and will be unable to be linked back to a specific individual.

15.0 Study Monitoring

15.1 Your study requires either Data and Safety Monitoring Plan (DSMP) or a Data and Safety Monitoring Board (DSMB).

- (●) DSMP
- ( ) DSMB
- ( ) Both
- ( ) Not Applicable

A DSMP should describe the plan to monitor the data to verify that the data are collected and analyzed as specified in the protocol. Include who will conduct the monitoring, what will be monitored, and the frequency of monitoring. It should also include the plan to ensure the safety of subjects

Participant Safety Monitoring Plan:
To ensure the safety of participants the PI will:

1. Monitor the conduct of the protocol per the approved study plan and ensure protection of human participants. This may involve periodic review of medical records and/or research files of enrolled participants.
2. Review and keep abreast of adverse events and protocol deviations that occur during the research.
3. The PI will review and sign adverse event logs/reports, protocol deviation (PD) logs /reports, and continuing reviews (CR)/annual progress reports.
4. If there is concern about the welfare of enrolled participants, the PI will stop the research study in progress, remove individual participants from a study, and take whatever steps necessary to protect the safety and well-being of research participants until the IRB can assess the situation.
5. Ensure that all study team members keep current required human subjects research trainings which require renewal every 3 years.

If an adverse event or protocol deviation occurs, it will be evaluated by the Principal Investigator and appropriate actions will be taken as outlined in Section 16.0 Reportable Events. In the case of an emergency, first responders will be called. In order to address the challenge of early identification of an increased risk of a known adverse event, all adverse event data will be tracked and evaluated.

On-site physicians will monitor the progress and health of the participants alongside our Principal Investigator. Participants can elect to withdraw from the study at any time. Participants may also be taken out of the study at any point if a research provider (or one of their treating providers) determines that it is no longer safe for them to continue with the study. If a participant elects to drop out of the study or is withdrawn for safety reasons, they will resume standard of care treatment with their assigned health provider(s).

Data Monitoring Plan:
Data will be collected and stored in both paper CRF and electronic format as described previously in protocol section 10.14 Data Management. In addition to data quality and data validation checks done continually by REDCap for electronic format data, authorized MIRROR staff will perform routine checks of the coded electronic data entered into REDCap and Teleray to ensure that data has been properly input and that data entry is consistent with expected values. The local PI will ensure that paper research forms and the electronic Master List are completed and securely stored in accordance with stated protocol procedures.

Please see protocol Section. 14.3 Confidentiality Protections and 14.5 Privacy for Subjects for additional information regarding how we will protect participant privacy and confidentiality throughout this study.

16.0 Reportable Events

16.1 Reportable Events: Consult with the research office at your institution to ensure requirements are met. Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event.

Consult with the research office at your institution to ensure requirements are met

• Describe plans for reporting expected adverse events. Identify what the expected adverse events will be for this study, describe the likelihood (frequency, severity, reversibility, short-term management and any long-term implications of each expected event)

• Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the research protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event

AEs/SAEs/UPIRTSOs:
The study overall is considered to be minimal risk for study participants, defined as not substantially above what would be encountered in everyday life including provision of routine medical care for the condition of knee OA. Potential risks are preventable by ensuring that appropriate and rigorous screening procedures are in place, and risk mitigation procedures (e.g., wearing appropriate eye protection) are utilized. Based on clinical use of this technology, and reports from other research studies, the risk of expected adverse events is low.

However, all reportable events, regardless of severity, will be reported to the Principal Investigator. The Principal Investigator will review all adverse events.

All Serious Adverse Events (SAEs) that are unexpected and related, or possibly related, to study participation will be reported to the IRB via telephone or email within 24 hours of discovery and a complete written report via eIRB will follow within 5 business days.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOs) will be reported to the IRB via telephone or email within 24 hours of discovery and a complete written report via eIRB will follow within 5 business days.

Unexpected (but not serious) adverse events (AEs) occurring in subjects which, in the opinion of the PI, are related or possibly related to study participation AND places subjects or others at a greater risk of harm that was previously known or recognized in the protocol will be reported to the IRB via telephone or email within 24 hours of discovery and a complete written report via eIRB will follow within 5 business days.

Expected AEs/SAEs and AEs/SAEs that are not related or not possibly related to study participation will be tracked by the local study team using an Adverse Event Tracking Log and reported to the IRB at the time of continuing review or, if applicable, at study closure.

Continuing Review (CR) Progress Reports are generally performed on a 12-month cycle. More frequent Progress Reports may be required at the discretion of the IRB.

Protocol Deviations:
All protocol deviations, both major and minor, will be reported to the Principal Investigator. The Principal Investigator will review all protocol deviations.

Major protocol deviations, as determined by the Principal Investigator, will be promptly reported to the IRB via telephone or email within 24 hours of discovery and a complete written report will follow within 5 working days.

Minor protocol deviations will be tracked by the local study team using a Protocol Deviation Log and reported to the IRB at the time of continuing review or, if applicable, at study closure. Follow up visits that occur outside of the windows stated in protocol will be considered minor protocol deviations.

17.0 Equipment/non-FDA Regulated Devices

17.1 Does the study involve the use of any unique non-medical devices/equipment?

○ Yes ◉ No

18.0 FDA-Regulated Products

18.1 Will any drugs, dietary supplements, biologics, or devices be utilized in this study?

- ☐ Drugs
- ☐ Dietary Supplements
- ☑ Biologics
- ☑ Devices
- ☐ N/A

18.2 Drugs, Dietary Supplements and Biologics/Vaccines details:

- ☑ Are drug(s) in this research being used in accordance to the approved labeling?
- ☐ Are drug(s) in this research being used in a manner other than its approved labeling?

Enter Dietary Supplements and Biologics/Vaccines in the Drug Information table. Complete all relevant fields in the table ("Protocol Drug Details" screen). If the question is not relevant, leave the question blank and/or do not change the default selection.

View Details	Drug Name	FDA Approved	A new drug or a new use of approved drug:	IND Number
⊟	**Trade Drug Name:** Platelet Rich Plasma (PRP) **Generic Drug Name:** **Investigational Drug Name:**	No	No	

Trade Drug Name:	Platelet Rich Plasma (PRP)
Generic Drug Name:	
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	autologous
Is the drug supplied at no cost?	Yes
Is the Drug FDA Approved:	No
Is this a new drug or a new use of an already approved drug	No
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A

IND details:	N/A
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	Blood products such as PRP fall under the purview of FDA's Center for Biologics Evaluation and Research (CBER). CBER is responsible for regulating human cells, tissues, and cellular and tissue-based products. The regulatory process for these products is described in the FDA's 21 CFR 1271 of the Code of Regulations. Under these regulations, certain products including blood products such as minimally manipulated, autologous PRP are considered exempt.
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	N/A
Dose Range:	
Frequency:	1
Route of administration:	Intra-articular injection
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	N/A
Identify who will be preparing the investigational drug /biologic for administration and describe in detail how it will be prepared:	The PRP will be prepared following standard technique by drawing 60cc blood from the participant through venipuncture, and spinning the blood sample in a centrifuge (for approximately 17 minutes), adjusting for leukocyte poor-platelet rich plasma (LP-PRP). This sample will be prepared by the study provider (physician assistant or physician). Any leftover blood will be safely discarded per standard protocols.
Indication(s) under Investigation:	Knee osteoarthritis
Where will the drug be stored	N/A
Drug Storage Restrictions (including temperature, etc.):	N/A
Administration Instructions:	Prior to the injection, the area will be sterilely prepared and anesthetized with either ethyl chloride spray or lidocaine (limited to the cutaneous and subcutaneous layer, so as not to alter the synovial contents). Then, the participant will receive LP-PRP injection in the affected knee area under ultrasound guidance. Qualified study providers will inject 2-5cc LP-PRP using an 18-gauge 1/5-inch needle for both aspiration and subsequent injection. Study providers will select the injection portal they are most comfortable with, in order to achieve an accurate intra-articular injection.
Possible Untoward Effects, Their Symptoms & Treatment:	Common side effects: • Localized pain • Soreness • Bruising • Tenderness Injection aftercare: • Ice injection site, as needed • Avoid strenuous/aggressive activities for 2-3 days • Avoid NSAIDS and COX-2 inhibitors for 2 weeks
Potential or Actual Antidotes for Excessive or Adverse Drug Effect:	N/A
Contraindications and Interactions, If Known:	N/A
Investigators Authorized to Prescribe:	N/A

18.3 Device Details:

☑ Are device(s) in this research being used in accordance to the approved labeling?
☐ Are device(s) in this research being used in a manner other than its approved labeling?

When adding a device indicate in the details section of the device if the use is either used in accordance to the approved labeling or in a manner other than it's approved labeling

View Details	Device Name
⊟	LightForce® XPi therapy laser

Manufacturer/Supplier of Device	LiteCure, DJO Global, Envois
Where will the Devices Be Stored	In the research area
Will Devices be supplied at no Cost	No
Is this a HUD (HDE)	No
HDE Number	N/A
Who holds the IDE	N/A
IDE details	N/A

18.4 Reporting Requirements for FDA-regulated research under IND and IDE:

Describe the process for complying with FDA regulatory requirements for adverse event reporting and adverse device effects reporting to the sponsor

Minimally manipulated autologous PRP is considered an exempt blood product.

The PI will be responsible for reporting any unanticipated adverse effects and unanticipated problems to the FDA for the device.

18.5 Sponsor (organization/institution/company):

☑ N/A

If applicable, provide sponsor contact information:

19.0 Research Registration Requirements

19.1 ClinicalTrials.gov Registration:

○ Registration is not required
◉ Registration pending
○ Registration complete

19.2 Defense Technical Information Center Registration (Optional):

◉ Registration is not required
○ Registration pending

Registration complete

20.0 References and Glossary

20.1 References:

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20.2 Abbreviations and Acronyms:

Acetylsalicylic Acid (ASA)
Active-Duty Service Member (ADSM)
Advanced Encryption Standard (AES)
Adverse Event (AE)
American College of Rheumatology (ACR)
American National Standards Institute (ANSI)
Anteroposterior (AP)
Associate Investigator (AI)
Binary Digit (bit)
Case Report Form (CRF)

Celsius (C)
Center for Biologics Evaluation and Research (CBER)
Centimeter (cm)LLC
Clinical Laser Safety Officer (CLSO)
Common Access Card (CAC)
Complete Blood Count (CBC)
Composite Health Care System (CHCS)
Continuing Review (CR)
Corticosteroid Injection (CSI)
Cubic Centimeter (cc)
Cyclooxygenase-2 (COX-2)
Datagram Transport Layer Security (DTLS)
Date of Birth (DOB)
Defense and Veteran's Pain Rating Scale (DVPRS)
Defense Enrollment Eligibility Reporting System (DEERS)
Defense Health Agency (DHA)
Defense Health Agency Administrative Instruction (DHA-AI)
Delaware (DE)
Deoxyribonucleic Acid (DNA)
Department of Clinical Investigations (DCI)
Department of Defense (DoD)
Department of Defense Issuances (DoDI)
Department of Pathology and Area Laboratory Services (DPALS)
Dipotassium Ethylenediaminetetraacetic Acid (K2 EDTA)
Electronic Medical Record (EMR)
Enzyme-Linked Immunoassay (ELISA)
Eppendorf tube (ept)
Food & Drug Administration (FDA)
Gram (g)
Hash-based Message Authentication Code- Secure Hash Algorithm 1 (HMAC-SHA1)
Healthcare Technology Management and Sustainment (HTMS)
Health Insurance Portability and Accountability Act (HIPAA)
History (Hx)
Holistic Health and Fitness (H2F)
Human Chorionic Gonadotropin (HCG)
Human Research Protections Office (HRPO)
Identification (ID)
Information Technology (IT)
Informed Consent Form (ICF)
Institutional Review Board (IRB)
Internet Engineering Task Force (IETF)
Joint Program Committee (JPC)
Joules (J)
Knee Injury and Osteoarthritis Outcome Score (KOOS)
Knee osteoarthritis (KOA)
Laser Safety Committee (LSC)
Laser Safety Officer (LSO)
Leukocyte Poor-Platelet Rich Plasma (LP-PRP)
Limited Liability Company (LLC)
Madigan Army Medical Center (MAMC)
Microliter (µL)
MicroRNA (miRNA)
Military Health System (MHS)
Milliliter (mL)
Musculoskeletal Injury (MSI)
Musculoskeletal Injury Rehabilitation Research for Operational Readiness (MIRROR)
Non-Steroidal Anti-Inflammatory Drug (NSAID)
Osteoarthritis (OA)
Osteoarthritis Research Society International (OARSI)
Personally Identifiable Information (PII)
Photobiomodulation treatment/therapy (PBMT)
Physical Medicine & Rehabilitation (PM&R)
Physical Therapy (PT)
Platelet-Rich Plasma (PRP)
Post-traumatic knee osteoarthritis (PTOA)
Principal Investigator (PI)
Protected Health Information (PHI)
Protocol Deviation (PD)
Quantile-Quantile (QQ)
Quantitative Polymerase Chain Reaction (qPCR)

Research Coordinator (RC)
Research Electronic Data Capture (REDCap)
Ribonucleic Acid (RNA)
Secure Access File Exchange (SAFE)
Secure Real-time Transport Protocol (SRTP)
Secure Sockets Layer (SSL)
Serious Adverse Event (SAE)
Single Assessment Numeric Evaluation (SANE)
Synovial Fluid (SF)
Standard of Care (SOC)
Tactical Human Optimization, Rapid Rehabilitation and Reconditioning (THOR3)
Transport Layer Security (TLS)
Ultraviolet (UV)
Unanticipated Problem Involving Risks to Subjects or Others (**UPIRTSO)**
Uniformed Services University (USU)
Uniformed Services University Information Technology (USU IT)
United States (US)
U.S. Army Medical Research and Development Command (USAMRDC)
Veterans Rand 12 Item Health Survey (VR-12)
Watts (W)
X-radiation (X-ray)