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TITLE: Timing of Surgery and Rehabilitation to Optimize Outcome for Patients with Multiple Ligament Knee Injuries: A Multicenter Clinical Trial

PRINCIPAL INVESTIGATOR: James Irrgang PT PhD ATC FAPTA

RECIPIENT: University of Pittsburgh
Pittsburgh, PA 15213

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James Irrgang PT PhD ATC FAPTA

Email: irrgangjj@upmc.edu

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14. ABSTRACT

Multiple ligament knee injuries (MLKIs) are complex injuries that represent a spectrum of injury ranging from disruption of two ligaments (one cruciate ligament and one collateral ligament) to all four ligaments (both cruciates and both collateral ligaments). Multiple ligament knee injuries are frequently associated with concomitant injuries to nerves, vessels, tendons, cartilage and menisci. Non-operative management of MLKIs results in poor outcomes; however there is no consensus on the optimal surgical approach for MLKIs. Level III evidence suggests that in comparison to delayed surgery, early surgical management of MLKIs leads to better clinical outcomes, but is associated with a higher risk of loss of motion and joint contracture. Suboptimal outcomes for treatment of MLKIs include persistent pain, stiffness, residual instability and laxity, loss of motion and limited ability to perform demanding activities associated with military training, heavy physical labor and sports.

15. SUBJECT TERMS-

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

   The overall purpose of this Clinical Trial Development Award (CTDA) is to plan a multicenter randomized clinical trial is to investigate the effects of timing of surgery and rehabilitation to optimize clinical outcome and return to duty/activity for military personnel and civilians with a multiple ligament knee injury (MLKI). We hypothesize that early surgery and early initiation of post-operative rehabilitation will lead to improved outcomes in terms of: 1) return to duty/work and sports, 2) patient-reported and performance-based measures of physical function and health-related quality of life; 3) restoration of normal laxity and range of motion with 4) no increased risk of complications. The overarching objectives for the CTDA are to: 1) further develop the research network to ensure access to a population of individuals with a MLKI injury that is necessary for successful recruitment of the required number of subjects; 2) finalize the experimental design including issues related to subject eligibility, randomization and outcome measurement; 3) develop clinical protocols for surgery and post-operative rehabilitation; 4) finalize the required sample size and develop the statistical analysis and data management plans; 5) develop a clinical and safety monitoring plan; 6) establish a governance structure to oversee conduct of the study; 7) develop a site monitoring plan that includes guidelines for closing and adding sites; and 8) develop a transition plan to move to implementation of the clinical trial.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

   Multiple ligament knee injury; timing of surgery; timing of post-operative rehabilitation; optimizing return to activity/duty; patient-reported outcome.

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

   What were the major goals of the project?

   Under the approved SOW, the project had the following major goals:
   1) Develop Research Network for Multicenter Clinical Trial
   2) Finalize Experimental Design
   3) Develop Clinical Protocols
   4) Finalize Sample Size and Develop Statistical Analysis & Data Management Plan
   5) Establish Governance Structure to Oversee Study Management
   6) Develop Clinical and Safety Monitoring Plan
   7) Develop Site Monitoring Plan
   8) Develop Transition Plan to Move to Clinical Trial
   9) Prepare and Submit Application for Clinical Trial Award to Conduct Trial

What was accomplished under these goals?

1) Develop Research Network for Multicenter Clinical Trial (Task 1)

a) During this project period 23 sites have confirmed participation in the research network to contribute patients to a clinical trial that will evaluate the effects of timing of surgery and post-operative rehabilitation for persons with a MLKI. Investigators at all sites have expressed interest and commitment to participating in the multicenter clinical trial and have participated in the regular investigator conference calls and two in-person investigators' meetings. The 23 clinical sites include 5 U.S. Military Medical Centers; 15 U.S. Civilian Medical Centers, and 3 Canadian Medical Centers).

b) The criteria and protocol for the medical record review were established in the fall of 2015. The data collection form and data dictionary were finalized and distributed to the sites. As of the date of this report, IRB approvals for chart review activities have been obtained from 16 sites. Chart review data has been collected from 13 sites.

c) Conference calls with investigators from the collaborating clinical sites have been held on a monthly basis. During these calls the investigators discuss updates of the contract process, status of IRB review and approvals, content and procedures related to the review of medical records, issues related to the design of the clinical trial (subject eligibility criteria, study interventions, primary and secondary outcomes, etc.), and the overall study governance structure.

d) Two Investigators' Meeting were held during this project period. The first was March 1-2, 2016 in Orlando, FL; the second was July 7, 2016 in Colorado Springs, CO. The meetings covered the following topics: specific aims for the clinical trial; MLKI classification system; patterns of MLKIs; eligibility criteria; research design; available sample size and power calculations; randomization procedures; primary and secondary outcomes; definition of surgical and rehabilitation interventions; data management and statistical analysis; surgical case report forms; and complications and adverse events.

2) Finalize Experimental Design and Develop Clinical Protocols (Task 2 and Task 3)

a) The study objectives were developed and approved by the study investigators. They include:

Objective 1: Determine the combined effects of timing for surgery and rehabilitation for a MLKI on time to return to duty/work and sports and patient-reported physical function.

Objective 2: Determine the effects of timing for rehabilitation for a MLKI for which surgical timing has been predetermined on time to return to duty/work and sports and patient-reported physical function.

Objective 3: Enroll those that have a MLKI that precludes randomization to surgery or rehabilitation into parallel prospective observational study.

b) Investigators finalized the eligibility criteria for each of the study objectives. The eligibility criteria include:
Male and female military personnel and civilians between the ages of 14 and 65 with a MLKI (defined as a complete grade III injury of 2 or more ligaments) without a history of prior knee ligament reconstruction that do not have associated poly-trauma or a traumatic brain injury that limits their ability to participate in their care are eligible to participate in the proposed integrated studies.

To address Objective 1, individuals with a MLKI that present within 4 weeks of injury will be randomized to early (within 6 weeks of injury) or delayed (12 to 16 weeks after injury) surgery and early rehabilitation (weightbearing [WB] and unrestricted range of motion [ROM] exercises starting first week after surgery) vs. delayed rehabilitation (non-WB and limited ROM exercises [0° to 45°] for the first four post-op weeks).

To address Objective 2, subjects with a MLKI that present greater than 4 weeks after injury, require use of an external fixator to maintain reduction of the knee or have an injury that precludes randomization to delayed surgery as well as those that refuse randomization to timing of surgery will be eligible to participate the trial that compares only early vs. delayed rehabilitation.

For Objective 3, we will enroll individuals with a MLKI that can not be randomized to early rehabilitation including those unable to WB on the opposite limb, require a surgical procedure that precludes early ROM and WB (i.e. meniscus root repair, extensor mechanism or injury, vascular injury) as well as those that refused randomization to timing of rehabilitation in to the observational study.

c) The primary and secondary outcomes of the clinical trial were developed by the investigators.

The primary outcomes of the proposed studies will be clinical trial will be time to return to duty/work and sports activity and patient-reported physical function, as measured by the Multiple-Ligament Quality of Life Physical Function Subscale.

The secondary outcomes will include additional patient-reported outcomes, complications, and rates of re-injury.

d) The Executive Committee in conjunction with the study investigators have developed and agreed upon the definitions for early surgery (repair and/or reconstruction within 6 weeks of injury) and delayed surgery (repair and/or reconstruction 12 to 16 weeks after injury).

e) The Rehabilitation Committee in conjunction with the study investigators have developed and agreed upon post-operative rehabilitation guidelines early and delayed post-operative rehabilitation groups, as well as the universal rehabilitation procedures that will apply to all subjects regardless of group assignment.

3) Finalize Sample Size and Develop Statistical Analysis & Data Management Plan (Task 4)

a) Based on our preliminary retrospective study during this planning project, we estimate that across 25 clinical sites there will be 1355 MLKIs over a 2-year recruitment period. After the exclusions for participation in the trial that randomizes timing of surgery and rehabilitation (Objective 1), we estimate that there will be approximately 520 eligible individuals with a MLKI that present to orthopaedics within four weeks of injury, making it possible to perform surgery within 6 weeks if randomized to early surgery. Assuming that 70% of the eligible subjects agree to participate in the study, this would provide a sample size of 90 per group. This sample size would provide 79%-91% power to detect a 15% absolute difference (α=0.05) in the rate of return to duty/work for the main effects (n=180 for each arm) for timing of surgery or timing of rehabilitation, assuming the delayed arm has a return rate of 30% to 70%. Additionally, we would have 80% power to detect a 17% to 22% difference between the early surgery/early rehabilitation group (n=90) compared to any of the other 3 groups with return to activity rates from 30%-70%.

b) For the trial in which subjects are only randomized to early vs. delayed rehabilitation (Objective 2), 165 subjects randomized to each group (330 subjects), would provide 80% power to detect an absolute difference of 15% between the groups assuming the delayed rehabilitation group has a return to duty/work and sports rate of 60%.

c) For Objectives 1 and 2 we will use survival analysis for time to return to activity and linear mixed models for patient reported physical function to account for repeated measures. Assuming there is no interaction between the two factors for the trial that randomizes both surgery and rehabilitation, we will focus on testing the main effects. Analyses for Aim 3 will use the same statistical techniques but will focus on building parsimonious models that explain variation in outcomes. Time to event analyses will provide greater power by comparing time to event curves rather than a single time point and including patients lost to follow up prior to 2 years.

d) An electronic data management system has been developed by collaborators at Carolinas Healthcare using the REDCap data capture system. Data collection forms have been built for forms related to clinical findings, surgical findings and procedures, patient reported outcome measures, adverse events, complications, and subject tracking. During the proposed clinical trial this database will be utilized by all collaborating sites to collect trial data in real-time.

4) Establish Governance Structure to Oversee Study Management (Task 5)

a) The overall governance structure for the clinical trial was established during the Clinical Trial Development Award. This included establishing the purpose, structure, function and responsibilities of the Executive Steering Committee. The Executive Steering Committee will consist of 10 members representing military and civilian sites, as well as geographic location. Members of the committee are James Irrgang (Chair), Volker Musahl (Co-Chair), Travis Burns, Christopher Harner, Bruce Levy, Andrew Lynch, Charity Moore, Brett Owens, Robert Schenck, Daniel Whelan.

b) The Executive Steering Committee established and defined the purpose, structure and function of the following committees: Forms Committee, Publications & Ancillary Studies Committee, Rehabilitation Committee, Quality Control Committee, Recruitment Committee, and Adverse Events Adjudication Committee. Interest in serving on one of the committees has been obtained and membership of the committees has been established.

c) Guidelines for papers summarizing the primary aims of the study, secondary analysis studies, ancillary studies, and abstracts were developed by the Publications & Ancillary Studies Committee. These guidelines were presented to all investigators at the July 2016 Investigator Meeting in Colorado Springs, CO.

d) The Adverse Events Adjudication Committee will include three to five individuals external to the study investigators and will be responsible for reviewing and adjudicating any and all adverse events. The composition of the Adverse Events Adjudication Committee will be established prior to beginning the full clinical trial.

5) Develop Clinical and Safety Monitoring Plan (Task 6)

a) Clinical and Safety Monitoring Plans are currently being developed for the full clinical trial -- including identification of medical monitor and data safety monitoring board.

6) Develop Site Monitoring Plan (Task 7)

a) Site Monitoring Plans are currently being developed for the full clinical trial -- including developing criteria for opening and closing sites, and ongoing monitoring.

7) Develop Transition Plan to Move to Clinical Trial (Task 8)

a) Data collection forms have been developed for recording clinical findings, surgical findings and procedures, patient reported outcome measures, adverse events, complications, and subject tracking. The majority of these forms have been converted to electronic format for a web-based electronic data capture system using RedCAP as outlined in Task 4. Testing and debugging the electronic data capture system will be done in the coming year under the no cost extension that has been approved.

b) The Manual of Operations and related training materials will be developed in the coming year under the no cost extension that has been approved and will be distributed prior to the beginning of the clinical trial.

c) Institutional Review Board Approval will be obtained for the Coordinating Center (University of Pittsburgh) and also for each collaborating site where data will be collected. At this time the investigators are in discussion with the University of Pittsburgh IRB about the potential to use the University of Pittsburgh as a single, central IRB of record for all participating sites. At the time of implementation of the full clinical trial, all sites will obtain Department of Defense HRPO approval at that time. Additionally, research agreements between the University of

Pittsburgh and each external site will be executed prior to implementation, including data use agreements (DUAs) and material transfer agreements (MTAs), if applicable.

8) Prepare and Submit Application for CTA to Conduct Trial (Task 9)

a) The investigators submitted the Pre-Application to the Department of Defense Peer Reviewed Orthopaedic Research Program for the Integrated Clinical Trial Award (Funding Opportunity: W81XWH-16-PRORP-ICTA) on September 7, 2016. The investigators received the invitation to submit a full application on October 13, 2016. At this time the investigators are preparing to submit the full application and all required materials by the deadline on December 7, 2016.

What opportunities for training and professional development has the project provided?

Nothing to Report

How were the results disseminated to communities of interest?

Members of the Rehabilitation Committee, led by Dr. Andrew Lynch submitted a proposal describing the rehabilitation guidelines/protocol that was developed for the proposed clinical trial to the Combined Sections Meeting of the American Physical Therapy Section which has been accepted for presentation in February 2017. Additionally, the members of the Rehabilitation were invited to submit a paper describing the rehabilitation guidelines/protocol to Clinical Reviews in Musculoskeletal Medicine.

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

An extension request was submitted for this project. The investigators will continue the development of an application for a multicenter clinical trial to investigate the effects of timing of surgery and post-operative rehabilitation for the treatment of individuals with a multiple ligament knee injury. The application will be submitted to the Department of Defense Peer Reviewed Orthopaedic Research Program for an Integrated Clinical Trial Award (Funding Opportunity: W81XWH-16-PRORP-ICTA) by December 7, 2016.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them

There were significant delays in executing subcontract and data use agreements between the University of Pittsburgh and several of the external sites. Work on this project cannot be accepted by the University of Pittsburgh until these agreements are executed. At the time of this Annual Report, subcontracts for 15 sites that submitted data have been executed. Additionally, data use agreements for 2 sites have been executed. For the remaining sites, the Office of Research at the University of Pittsburgh has been preparing subcontracts for those sites that have obtained IRB approval.

At this time, there have been delays related to IRB approval for the military sites. To date, one military site has obtained IRB approval (San Antonio Military Medical Center). However, the remaining 3 military sites have IRB applications submitted and pending review.

It was also discovered during the grant period that each site would need to obtain Department of Defense Human Research Protection Office (HRPO) Approval. The work to obtain this approval is currently in process.

Changes that had a significant impact on expenditures

Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals.

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Nothing to Report.

  Books or other non-periodical, one-time publications.

  Nothing to Report.

  Other publications, conference papers, and presentations.

  Lynch AD, Bailey L; Burns T; Owens J; Irrgang JJ: Managing the Chaos: Rehabilitation of Multiple Ligament Knee Injuries. Accepted for presentation at the Combined Sections Meeting of the American Physical Therapy Association. San Antonio, TX, February 16, 2017

- **Website(s) or other Internet site(s)**

  Nothing to Report.

- **Technologies or techniques**

  Nothing to Report.

- **Inventions, patent applications, and/or licenses**

  Nothing to Report.

- **Other Products**

  Retrospective chart review data has been compiled from 13 sites participating in this project to determine injury and treatment patterns for multiple ligament knee injuries.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	James Irrgang
Project Role:	Principal Investigator
Nearest person month worked:	1
Contribution to Project:	Dr. Irrgang has been conducting monthly conference calls with all collaborators on the project. He has been in contact with each of the sites regarding IRB approval. He oversees all activity related to the project.

Name:	Volker Musahl
Project Role:	Co-Investigator
Nearest person month worked:	1
Contribution to Project:	Dr. Musahl has been instrumental in assisting with the surgical protocol for the study. He is conducting a review of patients that have undergone surgery for a MLKI from 2012 to 2014 to determine the timing of presentation and surgery, injury pattern, associated injuries, surgical procedures, outcomes and complications. He has participated in the monthly conference calls.

Name:	Charity Moore Patterson
Project Role:	Co-Investigator
Nearest person month worked:	1
Contribution to Project:	Dr. Moore-Patterson has been instrumental in assisting with study design and sample size calculations for the full clinical trial application. In addition, she oversaw the development of the electronic data capture system at Carolinas Healthcare System.

Name: Alicia Oostdyk
Project Role: Project Coordinator
Nearest person month worked: 3
Contribution to Project: Ms. Oostdyk has participated in the monthly conference calls. She is coordinating IRB approvals across all participating sites and has developed the case report forms and data base for the retrospective medical records review.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Change in Other Support for Irrgang JJ:

Title: **Predicting the Outcome of Exercise Therapy for Treatment of Rotator Cuff Tears**
Time: Commitment 7.5% (0.90 calendar months)
Role: Co-Principal Investigator
Supporting Agency: National Institute of Arthritis and Musculoskeletal and Skin Diseases
Name and Address of the Funding Agency's Procuring Contracting /Grant Officer:
Gail Hamilton
Democracy I, Room: 844
hamiltog@mail.nih.gov
Performance Period: 09/01/2016 – 05/31/2021
Level of Funding: $281,183
Brief Description of Project Goals:
The overall goal of the proposed project is to conduct a prospective observational cohort study to describe the effects of exercise therapy in terms of patient-reported and structural outcomes, as well as to identify predictors of these outcomes in patients with an isolated supraspinatus tear.

What other organizations were involved as partners?

Organization Name: Brown University
Location of Organization: Providence, RI, USA
Partner's contribution to the project: Collaboration and Other: data

Organization Name: Carolinas Healthcare
Location of Organization: Charlotte, NC, USA
Partner's contribution to the project: Collaboration

Organization Name: HealthPartners
Location of Organization: Minneapolis, MN, USA
Partner's contribution to the project: Collaboration and Other: data

Organization Name: *Hospital for Special Surgery*
Location of Organization: *New York City, NY, USA*
Partner's contribution to the project: *Collaboration and Other: data*

Organization Name: *Mayo Clinic*
Location of Organization: *Rochester, MN, USA*
Partner's contribution to the project: *Collaboration*

Organization Name: *TRIA/University of Minnesota*
Location of Organization: *Minneapolis, MN, USA*
Partner's contribution to the project: *Collaboration, and Other: data*

Organization Name: *University of Connecticut*
Location of Organization: *Storrs, CT, USA*
Partner's contribution to the project: *Collaboration, and Other: data*

Organization Name: University of Kentucky
Location of Organization: *Lexington, KY, USA*
Partner's contribution to the project: *Collaboration, and Other: data*

Organization Name: *University of New Mexico*
Location of Organization: *Albuquerque, NM, USA*
Partner's contribution to the project: *Collaboration, and Other: data*

Organization Name: *University of Virginia*
Location of Organization: *Charlottesville, VA, USA*
Partner's contribution to the project: *Collaboration, and Other: data*

Organization Name: *Washington University in St. Louis*
Location of Organization: *St. Louis, MO, USA*
Partner's contribution to the project: *Collaboration*

Organization Name: *San Antonio Military Medical Center*
Location of Organization: *San Antonio, TX, USA*
Partner's contribution to the project: *Collaboration and Other: data*

Organization Name: *Western University / Fowler Kennedy Sports Medicine Clinic*
Location of Organization: *London, ON, Canada*
Partner's contribution to the project: *Collaboration, and Other: data*

Organization Name: *St. Michael's Hospital*
Location of Organization: *Toronto, ON, Canada*
Partner's contribution to the project: *Collaboration*

Organization Name: *Nova Scotia Health Authority*
Location of Organization: *Halifax, NS, Canada*
Partner's contribution to the project: *Collaboration, and Other: data*

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.