**AWARD NUMBER:** W81XWH-17-2-0060

**TITLE:** **Transfemoral Amputation Osseointegration Study (TFAOS)**

**PRINCIPAL INVESTIGATOR:** Jonathan Forsberg, MD, PhD

**RECIPIENT:** Henry M Jackson Foundation, Bethesda, MD

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**TYPE OF REPORT:** **Annual**

**PREPARED FOR:** U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**

Henry M. Jackson Foundation, for the Adv. of Mil. Med.
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**9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)**

U.S. Army Medical Research and Materiel Command
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Approved for Public Release; Distribution Unlimited

**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**

This is a 5-year, prospective multisite cohort study, evaluating a device that is FDA approved under a Humanitarian Device Exemption. The study is being conducted at Walter Reed National Military Medical Center and the University of California, San Francisco. This non-randomized, longitudinal study will use each study participant as his or her own control and test the hypothesis that osseointegration results in improvements in the primary and secondary outcomes. As of year 4, there have been 41patients at WRNMMC and 9 at the University of California San Francisco. Patient-reported outcomes continue to be collected as scheduled. We are doing our best to collect functional outcomes, although some pandemic-related clinical research restrictions remain in place.

**15. SUBJECT TERMS**
Osseointegration, transfemoral, amputee, OPRA, functional outcomes, titanium implant, amputation

| **16. SECURITY CLASSIFICATION OF:** | | | **17. LIMITATION OF ABSTRACT** | **18. NUMBER OF PAGES** | **19a. NAME OF RESPONSIBLE PERSON** |
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**Standard Form 298 (Rev. 8-98)**
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## 1.INTRODUCTION:

**Transfemoral Amputation Osseointegration Study (TFAOS)** This is a 5-year, prospective multisite cohort study, evaluating a device that is FDA approved under a Humanitarian Device Exemption. Transfemoral amputees will be recruited using an existing, robust, network of combat related upper extremity amputees maintained at the Military Advanced Training Center, Walter Reed National Military Medical Center (WRNMMC), and at the University of California, San Francisco (UCSF). This non-randomized, longitudinal study will use each study participant as his or her own control, and test the hypothesis that osseointegration results in improvements in the primary and secondary outcomes listed below. In conducting this study, we will measure a comprehensive set of physiologic parameters, and collect outcome measures that ensure that the results of this trial and the safety profile of the Osseoanchored Prosthesis for the Rehabilitation of Amputees (OPRA) implant system are comparable to previous studies, which is important when applying this FDA-approved— but emerging— technology to a new, predominately military, patient population. The study will investigate the function, health related quality of life, and safety outcomes following placement of the OPRA device in patients with transfemoral amputations.

## 2.KEYWORDS:

Osseointegration, implant, titanium, OPRA, functional outcomes, transfemoral, amputee, amputation

## 3.ACCOMPLISHMENTS:

**What were the major goals of the project?**

| Major Task 1: Study Preparation | Timeline (mnths) | Status |
|---|---|---|
| subtask 1: Initiate subaward contract | 1-4 | complete |
| Subtask 2: Obtain local IRB Approval (UCSF) | 1-8 | complete |
| Subtask 3: Obtain local IRB Approval (WRNMMC) | 1-8 | complete |
| Subtask 4: Obtain secondary approval (HRPO) for WRNMMC site | 3-12 | complete |
| Subtask 4a: Obtain secondary approval (HRPO) for UCSF site | 3-12 | complete |
| **Major Task 2: Project Initiation and enrollment** | **Timeline (mnths)** | **Status** |
| subtask 1: Enroll patients at WRNMMC (41 implants) | 3-36 | complete |
| Subtask 1a: Enroll patients at USCF (9 implants) | 3-36 | complete |
| Subtask 2: Conduct surgeries (S1) | 3-36 | complete |
| Subtask 3: Conduct surgeries (S2) | 6-36 | ongoing |
| **Major Task 3: Patient Rehabilitation and Prosthetic fitting** | **Timeline (mnths)** | **Status** |
| subtask 1: Patient rehabilitation | 3-60 | ongoing |
| Subtask 1a: Establish weight bearing protocol and fit new prosthetics | 3-60 | ongoing |
| **Major Task 3: Patient Rehabilitation and follow-up** | **Timeline (mnths)** | **Status** |
| subtask 1: Conduct patient rehabilitation and collect functional outcomes data (Pre., 3,6,9,12,24 months) | 3-60 | ongoing* |
| Subtask 1a: Collect AE and infection rate data on all patients | 3-60 | ongoing |
| **Major Task 4: Project Analysis and reporting** | **Timeline (mnths)** | **Status** |
| subtask 1: Conduct analysis of surgical outcomes and expected infection rates | 36-60 | In prep |
| Subtask 2: Conduct analysis of functional outcomes and compare to pre osseointegration functional status | 3-8 | |
| Subtask 3: Publish results in peer -reviewed journals and present at MHSRS. | 36-60 | |

* For patient safety and to allow full recovery, 3 month functional outcomes will no longer be collected.

**What was accomplished under these goals?**

- IRB approval WRNMMC-2017-0091; received 11/11/2017.
- HRPO Log Number A-20341.a secondary approval received 11/21/2017.
- WRNMMC has COMPLETED the initial enrollment target of 15 total patients enrolled.
- Ten patients have completed Stage II at WRNMMC as of Sept, 2018.
- IRB approval UCSF 15-16764; received 2/6/2018.
- IRB proposals UCSF 18-25404 and 18-25641; submitted 7/2/2018 as per HRPO request to split 15-16764 into separate Study (research) and Non-Study (HUD surgical) arms.
- IRB approval UCSF 18-25404 approval received 10/1/2018 and 18-25641 approval received 9/17/2018.
- UCSF protocols pending final HRPO approval.
- WRNMMC submitted an amendment to increase the number of patients at WRNMMC to 35 given the overwhelming demand from patients interested in participating in the research arm. Approved July 2018.
- In Year two
  - UCSF received HRPO approval.
  - UCSF began recruitment and enrollment.
  - UCSF commenced stage 1 surgical procedures and scheduled stage 2 surgical procedures.
  - WR continued enrollment and patient follow up. Currently 30 patients enrolled. The remaining 5 patients are expected to be enrolled within first 6 months of Y3.
  - WR submitted IRB continuing review.
  - OI Program presented early findings at Blast Injury Conference (London, UK) and MHSRS (Orlando, FL)
  - In Year three
  - Clinical Research activity paused, where necessary, due to COVID-19 pandemic beginning in March 2020. Although surgeries had resumed at WR by May 2020, many patients delayed surgery, and follow up appoints and continue to do so.
  - UCSF continued recruitment and enrollment though at a slower pace.
  - UCSF has resumed surgical procedures. Currently 6 patients enrolled.
  - 38 patients enrolled at WR. Eleven patients have completed the 2 yr follow-up at WR
- **In Year four**
  - Clinical Research activity resumed, subject to easing institution-specific pandemic-related restrictions.
  - WRNMMC and UCSF reached accrual goal of 50 subjects enrolled.
  - UCSF completed stage-1 surgery on 9 patients and stage-2 surgery on 8 patients.
  - Nineteen patients at WR have completed 2 years follow up
  - At WR, 4 patients enrolled have withdrawn, one patient after stage 1 surgery and 1 patient was deceased unrelated to study) prior completing 1 year of follow-up. Withdrawn patients are all not related to implant or surgical issues.
-

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

- Nothing to report

**How were the results disseminated to communities of interest?**

- Nothing to report due to curtailment of conferences secondary to the COVID-19 pandemic.

**What do you plan to do during the next reporting period to accomplish the goals?**

- Undertake stage-2 surgery on remaining UCSF patient, pending management of metastatic sarcoma.
- Continuing review of WRNMMC protocol (20117-0091)
- Continue to track rehabilitation, functional outcomes, and infection rates.
- Present/ publish on interim results (TFAOS patients with at least 12-month follow-up).
- Close out 2 year follow-up on as many patients as possible.

## 4.IMPACT:

**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:

- It was determined that the 3 month evaluation post S2 surgery should eliminate the functional (gait and biomechanics) components as patients seemed to require additional time to be comfortable and safe on their new prosthetic set up.
- Due to overwhelming interest from the combat wounded population, WRNMMC has increased the enrollment to 35 patients up from 15. UCSF enrollment targets remain the same.
- COVID 19 continues to impact patient follow-up, especially as most patients are not local to the study centers. Impact is expected to continue for the foreseeable future, although both sites are able to conduct follow-ups via video and functional outcomes testing if patients are willing to travel/ and make appointments.

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

The COVID-19 pandemic temporarily paused Clinical Research activities that were not essential to the health and well-being of subjects. Clinical Research activities have now been allowed to resume, such that we have been able to continue surgery as well as surgical, patient-reported, and functional outcomes assessments.

**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**

**Significant changes in use or care of human subjects**

- It was determined that the 3 month evaluation post S2 surgery should eliminate the functional (gait and biomechanics) components as patients seemed to require additional time to be comfortable and safe on their new prosthetic set up.
- No changes to report this period.
- Continuing Review was obtained at UCSF through 6/7/22 (18-25641) and 5/24/22 (18-25404).
- Continue Review was obtained at WRNMMC (2017-0091) Nov 2020 through to 11/10/2021.

**Significant changes in use or care of vertebrate animals**

Not applicable.

**Significant changes in use of biohazards and/or select agents**

Not applicable.

**6.PRODUCTS:**

**•Publications, conference papers, and presentations**

**Journal publications.**

- Osseointegration of Extremity Prostheses: A Primer for the Plastic Surgeon.

Souza JM, Mioton LM, Harrington CJ, Potter BK,Forsberg JA. Plast Reconstr Surg. 2020 Dec;146(6):1394-1403. doi: 10.1097/PRS.0000000000007364.

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

Nothing to report.

**Other publications, conference papers and presentations**.

"UCSF Osseointegration Program, and WRNMMC Program updates presented virtually at" DoD Osseointegration Program Annual "All Hands" (Virtual) Meeting, December 7, 2020.

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

https://orthosurgery.ucsf.edu/research/clinical-research/International.html
Details the UCSF international Center for Osseointegration Research, Education, and Surgery (iCORES) Program

https://orthosurgery.ucsf.edu/research/clinical-research/UCSF-Musculoskeletal-Research-Consortium-METRiCS.html
Describes the clinical and translational studies of the UCSF Musculoskeletal Research Consortium (METRiCS) Program.

- **Technologies or techniques**

- Nothing to report.

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

- **Other Products**

- Nothing to report.

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

### What individuals have worked on the project?

*Name: Jonathan Forsberg, MD*
*Project Role: Principle Investigator and Director*
*Researcher Identifier (e.g. ORCID ID):* 0000-0003-3835-0615
*Nearest person month worked: 3*
*Contribution to Project: CAPT Forsberg responsible for consenting patients and performing surgeries and overall project management.*

*Name: Benjamin K. Potter, MD FACS*
*Project Role: Associate Investigator*
*Researcher Identifier (e.g. ORCID ID):*
*Nearest person month worked: 3*
*Contribution to Project: COL Potter responsible for consenting patients and performing surgeries.*

*Name: Yessenia Gomez*
*'Project Role: Clinical Research Coordinator*
*Researcher Identifier (e.g. ORCID ID):*
*Nearest person month worked: 4*
*Contribution to Project: Ms. Gomez is responsible for coordinating patient appts, administering survey questionnaires.*

*Name: Angelica Melendez-Munoz*
*'Project Role: Clinical Research Coordinator*
*Researcher Identifier (e.g. ORCID ID):*
*Nearest person month worked: 12*
*Contribution to Project: Ms. Melendez-Munoz is responsible for coordinating patient appts, administering survey questionnaires*

*Name: Richard J. O'Donnell, MD*
*Project Role: UCSF – subaward Site PI*
*Researcher Identifier (e.g. ORCID ID):* 0000-0002-6366-2701
*Nearest person month worked: 6*
*Contribution to Project: Dr. O'Donnell responsible for consenting patients and performing surgeries and oversight of subaward site.*

*Name: Kristina Benirschke*
*'Project Role: Clinical Research Coordinator*
*Researcher Identifier (e.g. ORCID ID):*
*Nearest person month worked: 12*
*Contribution to Project: Ms. Benirschke is responsible for UCSF regulatory coordination, patient appts, administering survey questionnaires.*

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

- *Nothing to report*

**What other organizations were involved as partners?**

## 8.SPECIAL REPORTING REQUIREMENTS

**COLLABORATIVE AWARDS:**

**QUAD CHARTS:**

## 9.APPENDICES:

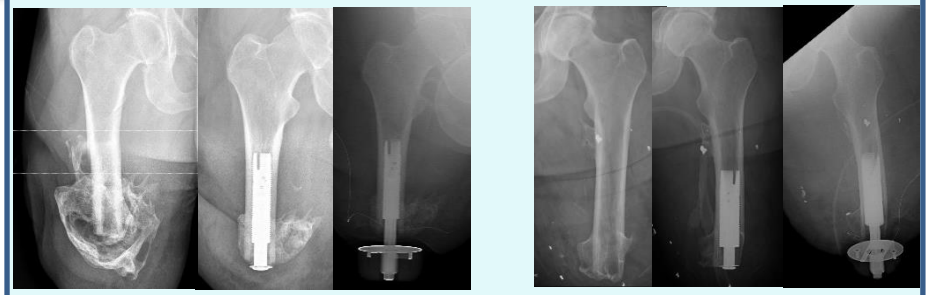
# Transfemoral Amputation Osseointegration Study (TFAOS)

**W81XWH-17-2-0060; Log# BA160465**

**PI: Forsberg, Jonathan** **Org:** Henry M Jackson Foundation **Award Amount:** $4,866,793

**Study Design: TFAOS is a** 5-year, prospective, nonrandomized, multi site clinical trial. The OPRA implant system (Integrum AB, Sweden) will be used to treat combat related transfemoral amputees who have difficulty utilizing standard prosthetics. In addition, to characterize implant-related complications, the investigators will assess "before and after" functional status, pain, and health related quality of life.

**Approach:** This clinical trial will be conducted at Walter Reed and UCSF using the OPRA transfemoral implant (FDA approved H080004 HUD#08-0197). Clinical and radiological assessments after completion of the surgical treatment will be performed pre-operatively, and at 3, 6, 12, and 24 months after completion of the surgical treatment. In addition, gait analysis and energy expenditure analysis will be performed and compared to baseline.



*Enrollment* 100% *of* 50 *total between WR and UCSF*

*Sixty two implant surgeries have been completed in the study on enrolled patients, including nine procedures at UCSF. Enrollees include 15 bilateral transfemoral amputees. Nine patients have completed 1 year follow- up and 19 have completed the 2-year study at WRNMMC.*

## Timeline and Cost

| Activities / Yr | 1 | 2 | 3 | 4 | 5 | Total |
|---|---|---|---|---|---|---|
| Regulatory Approval; Initial enrollment, site establishment | | | | | | |
| Complete enrollment | | | | | | |
| Patient Follow-up | | | | | | |
| Manuscript Preparation and summary findings | | | | | | |
| **Estimated Budget ($)** | $977k | $901K | $928k | $960k | $1100k | $4.86M |

**Goals/Milestones**

**Y1 Goals**

☑ Obtain and IRB/HRPO regulatory approvals
☑ Begin patient enrollment WRNMMC
☑ Establish Subaward/CRADA with UCSF
☑ HRPO approval for UCSF
☑ Establish regulatory approval at UCSF
☑ Begin patient enrollment UCSF

**Y2-3 Goals**

☑ Continue to enroll patients.
☑ Complete patient enrollment.

**Y4 Goals**

☑ Continue patient follow-up.
❑Present/ publish initial results- **in progress.**

**Y5 Goals**

☐ Complete all patient follow-up- **in progress.**
☐ Present/ publish final results- **in progress.**