AWARD NUMBER: W81XWH-17-2-0060

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

PRINCIPAL INVESTIGATOR: Jonathan Forsberg, MD, PhD

RECIPIENT: Henry M Jackson Foundation,
6720a Rockledge Dr, Suite 100,
Bethesda, MD 20817

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Transfemoral Amputee Osseointegration Study (TFAOS)

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6. AUTHOR(S)
CAPT Jonathan Forsberg, MD PhD
Richard J. O'Donnell, MD

E-Mail: jonathan.a.forsberg.mil@mail.mil

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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.
6720-A Rockledge Dr. STE 100
Bethesda, MD 20817

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
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12. DISTRIBUTION / AVAILABILITY STATEMENT

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)
Prescribed by ANSI Std. Z39.18

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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

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

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

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

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	complete
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	ongoing
Subtask 3: Publish results in peer -reviewed journals and present at MHSRS.	36-60	ongoing

* For patient safety and to allow full recovery, 3 months functional outcomes will no longer be collected. For ongoing tasks it is being funded on Federal funds from Uniformed Services University Health Sciences (USUHS).

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

- 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 9 patients enrolled.
- 41 patients enrolled at WR. Eleven patients have completed the 36 yr follow-up at WR

- **In Year Five**
  - WRNMMC and UCSF reached accrual goal of 50 subjects enrolled.
  - WRNMMC started a quarterly "Meet and Greet" where OI patients can meet with the surgeons and physical therapists to discuss and address concerns and questions patients may have.
  - OI data were disseminated at 2 non-scientific meetings (see below) and presented at 10 scientific meetings (see below) this year.
  - The OI Registry was presented at an osseointegration meeting that led to the onboarding of five new sites.
  - UCSF completed all stage 1 surgeries and 8 stage 2 surgeries, and 2 patients have completed 2 years follow up.
  - Thirty-two patients at WR have completed 2 years follow-up, only nine patients have not reached the 2-year follow-up, we will continue monitoring these patients. The nine remaining patients will complete the study in 2023.
  - 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?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

- Angelica Melendez attended a Clinical Research Coordinator prep course for a CRC certification.
- Jonathan Forsberg conducted a cadaver lab through Mast Labs, LLC for surgical training.
- Julio Rivera attended a statistical training course to learn new methodology to be applied in the osseointegration analyses.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

- Preliminary and simplified results were presented to osseointegration patients and their families at our quarterly Osseointegration Meet and Greet. Roughly 20 OI patients attended. These meetings will be ongoing for the foreseeable future.
- Preliminary data presented at the Society of Military Orthopaedic Surgeons – Extremity War Injuries where other military personnel, congress members, and private industry partners attended.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

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

Final report – Nothing to Report.

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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

This study has led to the development of the International Quality Amputee Registry for Osseointegration Surgery (IQAROS) where an additional eight non-military sites that have agreed to join. This registry will be the largest osseointegration database in the world with the purpose to facilitate collaborations and compare populations across the globe.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report.

5. **CHANGES/PROBLEMS:** The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official 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:

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Nothing to report

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

- No changes to report this period.

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: 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.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

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

Nothing to report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

- Forsberg and Potter. Early Outcome of Osseointegrated Implants in Transfemoral Amputations. June 2022, The Association of Bone and Joint Surgeons.
- Gladish et al. Trunk and Pelvis Movement in Sloped Walking for Servicemembers with Transfemoral Osseointegrated Prosthesis. Aug, 2022, American Society of Biomechanics and North American Congress of Biomechanics Joint Meeting.
- Severe et al. Osseointegrated Prosthesis use on Biomechanical Factors Associated with Knee Osteoarthritis: A Preliminary Analysis. Aug, 2022, American Society of Biomechanics and North American Congress of Biomechanics Joint Meeting.
- Acasio et al. Gait Symmatry and Stability in Servicemembers with unilateral Transfemoral Amputation Twelve Months After Osseointegration. Aug, 2022, American Society of Biomechanics and North American Congress of Biomechanics Joint Meeting.
- Harrington et al. Early Outcome of Osseointegrated Implants in Transfemoral Amputations. Aug. 2022, Military Health System Research Symposium.
- Mutreja et al. Human iMSCs-lade Photocurable Hydrogel for Improved Durability of the Skin/Implant Interface – An in vitro ad ex vivo Analysis. Aug. 2022, Military Health System Research Symposium.
- Mahon et al. Investigation of Mechanical Loading on Osseointegrated Implant Systems in Servicemembers with Transfemoral Limb Loss. Aug. 2022, Military Health System Research Symposium.
- Hendershot et al. Osseointegration Among Servicemembers with Transfemoral Limb Loss: Functional Outcomes within the First Year Aug. 2022, Military Health System Research Symposium.
- Rivera et al. TFAOS Outcomes Measures: An update. Aug. 2022, Society of military Orthopaedic Surgeons – Extremity War Injuries.
- Sabharwal et al. Responsiveness of Q-TFA and Select PROMIS Domains After Osseointegration in Transfemoral Amputees. Nov. 2022, Musculoskeletal Tumor Society.

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

  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

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**

  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to report.

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

  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. .

- **Other Products**

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Jonathan Forsberg, MD PhD
Project Role: Principle Investigator and Director Researcher
Identifier (e.g. ORCID ID): 0000-0003-3835-0615 *Nearest person month worked: 7.5*
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: 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: Julio A. Rivera, PhD
Project Role: Data Analyst
Researcher Identifier (e.g. ORCID ID): 0000-0002-3197-1745
Nearest person month worked: 12
Contribution to Project: Dr. Rivera was responsible for curation and analytics of the data.

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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to report

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Other.*

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (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.

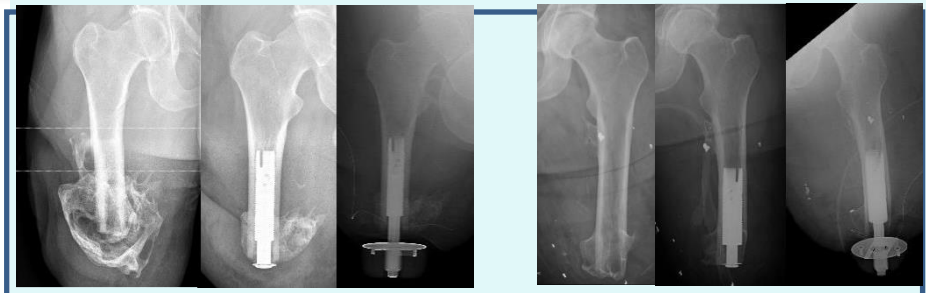
Transfemoral Amputation Osseointegration Study (TFAOS)

W81XWH-17-2-0060; Log# BA160465

PI: Forsberg, Jonathan **Org:** Henry M Jackson Foundation/USU **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 will complete their 2 year in 2023, and 32 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.**