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TITLE: Assessing the Comparative and Longitudinal Benefits of Vascularized Composite Allotransplantation of the Hand

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14. ABSTRACT

Hand transplantation can restore physical functions, including movement and sensation, and qualitative evidence from our ongoing research suggests that hand transplantation can also improve well-being and quality of life (QOL). However, there are risks to receiving hand transplant surgery and patients and doctors need valid information on QOL outcomes to weigh the risks and benefits of hand transplantation. This project will address the FY19 RTRP Focus Areas to (1) define/assess the benefits or value of hand transplant, including the relative value of hand transplantation compared to other treatment options and the benefits to social participation and satisfaction, and (2) to determine how psychosocial functioning changes over time within hand transplant recipients. We will conduct qualitative interviews with participants from four different clinical groups: (1) individuals who have undergone hand transplantation, (2) individuals with severe upper-extremity injuries who have undergone limb reconstruction surgery, (3) individuals with upper-extremity amputation who use prosthetic devices, and (4) individuals with upper-extremity amputation who use osseointegrated prosthetic devices. Furthermore, we will develop a set of consensus standardized outcomes measures that can be used at all clinical sites. The overall goal of this qualitative research study is to improve the methods used for evaluating outcomes after hand transplant surgery, leading to improved clinical decision-making and improved outcomes overall. This information may help hand transplant become a more feasible option for those with hand or arm amputations, which would allow more individuals to resume productive lives as a result. In additional to the University of Delaware and Walter Reed National Military Medical Center, the study has been approved at Brigham and Women's Hospital, Johns Hopkins University, the University of Pennsylvania, the University of Louisville, and Massachusetts General Hospital, for a total of 7 sites. Two more sites are in the processes of seeking regulatory approval: UCLA and Leeds NHS Trust in the United Kingdom. Data collection has been launched and, so far, 13 participants have completed interviews (4 osseointegrated prosthetic device users and 9 functional prosthetic device users).

15. SUBJECT TERMS

Hand Transplant, Patient reported outcomes, quality of life, vascularized composite allotransplantation, amputation, upper extremity

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1. INTRODUCTION:

Hand transplantation can restore physical functions, including movement and sensation, and qualitative evidence from our ongoing research suggests that hand transplantation can also improve well-being and quality of life (QOL). However, there are risks to receiving hand transplant surgery and patients and doctors need valid information on QOL outcomes to weigh the risks and benefits of hand transplantation. This project will address the FY19 RTRP Focus Areas to (1) define/assess the benefits or value of hand transplant, including the relative value of hand transplantation compared to other treatment options and the benefits to social participation and satisfaction, and (2) to determine how psychosocial functioning changes over time within hand transplant recipients. We will conduct qualitative interviews with participants from four different clinical groups: (1) individuals who have undergone hand transplantation, (2) individuals with severe upper-extremity injuries who have undergone limb reconstruction surgery, (3) individuals with upper-extremity amputation who use prosthetic devices, and (4) individuals with upper-extremity amputation who use osseointegrated prosthetic devices. Furthermore, we will develop a set of consensus standardized outcomes measures that can be used at all clinical sites. The overall goal of this qualitative research study is to improve the methods used for evaluating outcomes after hand transplant surgery, leading to improved clinical decision-making and improved outcomes overall. This information may help hand transplant become a more feasible option for those with hand or arm amputations, which would allow more individuals to resume productive lives as a result.

2. KEYWORDS:

Hand Transplant, Patient reported outcomes, quality of life, vascularized composite allotransplantation, amputation, upper extremity

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Study Specific Aims: (1) Assess the benefits of upper extremity (UE) vascularized composite allotransplantation (VCA) across emotional, social, physical, and functional domains. (1a) Understand the relative value of UE VCA compared to other treatment options (e.g., prosthetics, reconstruction, osseointegration). (1b) Document how UE VCA affects social roles, interactions, and functioning, including sense of self and wholeness. (2) Explore how psychosocial functioning and QOL change over time for UE VCA recipients. (3) Develop a consensus set of psychosocial and QOL outcome variables that can be assessed longitudinally across VCA clinical centers.

Statement of Work – Tasks and Subtasks	**% Complete**
Major Task 1: Prepare Regulatory and Administrative Documents for Data Collection	
Subtask 1.1: Finalize study procedures, consent form(s), and human subjects protocol	100
Subtask 1.2: Coordinate IRB protocol submission at UD	100
Subtask 1.3: Coordinate IRB protocol submission at WR	100

Statement of Work – Tasks and Subtasks	% Complete
Subtask 1.4: Coordinate IRB protocol submissions at other recruitment sites	85
Subtask 1.5: Coordinate protocol submission to OHRO at UD	100
Subtask 1.6: Coordinate protocol submission to OHRO at WR	100
Subtask 1.7: Coordinate protocol submission to OHRO at other sites, as necessary	85
Subtask 1.8: Coordinate administrative approvals (e.g., Data Sharing Agreements) among all sites, as necessary	75
Major Task 2: Conduct Baseline Interviews with Participants (n = 100)	
Subtask 2.1: Develop data collection platform (i.e., REDCap) and finalize interview procedures	100
Subtask 2.2: Recruit and screen participants	21
Subtask 2.3: Enroll and interview participants	13
Major Task 3: Analyze Data from Baseline Interviews	
Subtask 3.1: Conduct thematic qualitative analyses	0
Subtask 3.2: Conduct descriptive analyses of data from baseline interviews	0
Subtask 3.3: Evaluate and summarize results from Aim 1 analyses	0
Major Task 4: Conduct Longitudinal (1-year) Interviews with Participants (n = 100)	
Subtask 4.1: Develop longitudinal data collection platform and finalize interview procedures	0
Subtask 4.2: Re-contact and interview participants from Aim 1 data collection	0
Major Task 5: Analyze Data from Longitudinal (1-year) Interviews	
Subtask 5.1: Conduct thematic qualitative analysis from longitudinal interviews	0
Subtask 5.2: Conduct descriptive analysis of data from longitudinal interviews	0
Subtask 5.3: Evaluate and summarize results from Aim 2 analyses	0
Major Task 6: Identify and Disseminate a Set of Recommended Outcome Variables for VCA of the Hand	
Subtask 6.1: Develop a proposed set of outcome variables based on results from prior research and the Aim 1 results	0
Subtask 6.2: Share recommendations with partnering VCA collaborators and gather feedback	0
Subtask 6.3: Revise recommendations based on feedback	0
Subtask 6.4: Summarize recommendations and prepare for dissemination to VCA clinical sites	0

What was accomplished under these goals?

Major Task 1: Prepare Regulatory and Administrative Documentation

During year 1, a comprehensive multi-site study protocol was reviewed and approved by the UD IRB. UD confirmed with all participating sites that they were amenable to a single IRB model for this project, given the current DoD guidelines, and we approached all of the involved recruiting sites to gather information on the opportunity for a reliance agreement with the UD IRB. Subtasks 1.1 and 1.2 were completed in year 1.

In year 2, we obtained approval of our multi-site protocol from OHRO. We held multiple meetings individually with teams at all participating sites [Walter Reed (WR), University of Pennsylvania (Penn), the University of Louisville (UL), Johns Hopkins (JH), UCLA, Brigham and Women's Hospital (BWH), and Massachusetts General Hospital (MGH)], confirmed each site's willingness to have UD be the IRB of record, reviewed each site's and UD's regulatory and administrative documentation requirements, and created follow-up plans for each site. All steps between WR and UD were completed, including UD IRB approval. At BWH, cede approval was submitted. MGH, JH, and Penn each received local approval for reliance agreements. UL and UCLA submitted reliance agreement paperwork. In addition, staff at WR began the paperwork for a cooperative research and development agreement (CRADA) that will cover all involved sites and will include the necessary data sharing agreement(s). All subawards were established with participating sites. Subtask 1.5 was completed in year 2.
In year 3, reliance agreements were finalized and IRB and OHRO approvals were received at several additional partnering sites: WR, BWH, MGH, JH, Penn, and UL. We also came to an agreement with a site in the United Kingdom, Leeds Teaching Hospital NHS Trust, to pursue approval for Leeds to be added as a site on this project. During year 3, Co-PIs Tintle and Tulsky and Co-I Slotkin met with the investigators at Leeds and made arrangements for this to proceed, including determining the local ethics board's requirements needed for approval. Final IRB and OHRO approvals are still pending for UCLA and Leeds. Subtasks 1.3 and 1.6 were completed in year 3.
A no-cost extension (NCE) was requested and approved. Progress was made on the CRADA, including several rounds of internal and institutional reviews. The CRADA is still being finalized and we expect it to be fully executed in the NCE period.

<u>Major Task 2: Conduct Baseline Interviews with Participants</u>
During year 3, we developed the data collection procedures and platform in a REDCap ("Research Electronic Data Capture") database hosted by the UD Center for Human Research Coordination. We hired an experienced research interviewer at UD, Diana Pernigotti, MS, and trained her in the standardized procedures for qualitative and patient-reported outcome interviews for this study. We held meetings with five partnering sites (BWH, JHU, UL, UPenn, and WR) to provide them with instructions for recruiting and consenting participants, and for using UD's REDCap to enter screening and medical record information for the study. Subtask 2.1 was completed in year 3. Beginning in August 2023, we initiated the study interviews. During year 3, three sites were active with data collection: WR, UL, and UPenn. In addition, UD has been recruiting potentially eligible participants who agreed to be contacted after their participation in previous research studies done in Dr. Tulsky's lab. So far, across all sites, 46 individuals have been contacted for interest, 38 have been screened, and 28 were found to be eligible. Of these, 21 have provided informed consent and HIPAA authorization, and 13 participants have completed the Visit 1 ("baseline") interviews: 4 osseointegrated prosthetic device users and 9 functional prosthetic device users

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.

In the NCE period ("year 4") of this project, data collection will continue, including enrolling new participants, with the goal of completing baseline data collection, and conducting 1-year follow-up interviews with participants who have already completed their initial interviews. We will obtain all remaining IRB and OHRO approvals for recruiting patient participants from the two remaining sites (UCLA and Leeds), and we will finalize site-specific agreements for data sharing and other administrative concerns (i.e., CRADA).

4. **IMPACT:**

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

We have brought together many of the clinical sites involved in hand transplantation in the United States and the United Kingdom by forming the Transplant Outcomes Research Collaborative for the Hand (TORCH). Forming this consortium will have a major impact on the field because it will allow for improved synchronization of efforts for standardizing outcomes measures for upper extremity transplantation research and clinical care. This consortium will also allow our research team to recruit and enroll many of the available upper extremity transplant participants in the U.S., as well as osseointegration participants, both of which are extremely small populations nationwide.

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:

Changes in approach and reasons for change

Nothing to report.

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

Regulatory and administrative approvals have taken significantly longer than anticipated, due in part to the complexity of obtaining reliance agreements across multiple sites, all of which have idiosyncratic review and procedures for participant safeguards. To address this, we delayed expenditures in years 1 and 2, to assure funds are available to accomplish all project goals. We did not begin using grant funds until year 3, after regulatory approvals were received at several sites and recruitment could begin. We have worked closely with representatives from all sites to establish single IRB reliance agreements as well as a CRADA that will cover all sites.
To preempt concerns about meeting our sample size targets, we are working assiduously to add Leeds Teaching Hospitals in the United Kingdom as a recruitment site.

Changes that had a significant impact on expenditures

The delays in regulatory approvals have caused corresponding delays in spending for this project. However, we anticipate that the effect of this will be neutral on the budget over the life of the project.

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:

Publications, conference papers, and presentations

Nothing to report.

Journal publications.

Nothing to report.

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

Nothing to report.

Other publications, conference papers and presentations.

Nothing to report.

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

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Walter Reed National Military Medical Center (WRNMMC)

Name:	CAPT (sel) Scott Tintle, MD
Project Role:	Initiating PI at WR
ORCID ID:	0000-0003-0887-7600
Nearest person month worked:	1
Contribution to project:	no change
Name:	Christopher L. Dearth, PhD
Project Role:	Co-Investigator at WR
ORCID ID:	0000-0003-3701-0950
Nearest person month worked:	1
Contribution to project:	no change
Name:	Toby Perkins
Project Role:	Regulatory
ORCID ID:	none
Nearest person month worked:	1
Contribution to project:	no change
Name:	Angelica Melendez-Munoz
Project Role:	Research Coordinator
ORCID ID:	none
Nearest person month worked:	1
Contribution to project:	no change

University of Delaware (UD)

Name:	David Tulsky, PhD
Project Role:	Collaborating PI
ORCID ID:	0000-0002-4335-4509
Nearest person month worked:	1
Contribution to Project:	no change
Name:	Jerry Slotkin, PhD
Project Role:	Co-I
ORCID ID:	0000-0001-8199-3056
Nearest person month worked:	1
Contribution to Project:	no change
Name:	Callie Tyner, PhD
Project Role:	Co-I
ORCID ID:	0000-0003-2945-392X
Nearest person month worked:	1
Contribution to Project:	no change
Name:	Diana Pernigotti, MS

Project Role:	Research Associate at UD
ORCID ID:	0000-0002-1174-0069
Nearest person month worked:	2
Contribution to Project: Ms. Pernigotti recruited, consented, and conducted interviews with participants.	

Massachusetts General Hospital (MGH)

Name:	Curtis L. Cetrulo, MD
Project Role:	Collaborating PI
ORCID ID:	
Nearest person month worked:	1
Contribution to Project:	Dr. Cetrulo oversees all aspects of the project-related activities at MGH.

Brigham and Women's Hospital (BWH)

Name:	Simon G. Talbot, MD
Project Role:	Collaborating PI
ORCID ID:	
Nearest person month worked:	1
Contribution to Project:	Dr. Talbot oversees all aspects of the project-related activities at BWH.

The Johns Hopkins University (JHU)

Name:	Gerald Brandacher, MD
Project Role:	Collaborating PI
ORCID ID:	
Nearest person month worked:	1
Contribution to Project:	Dr. Brandacher oversees all aspects of the project-related activities at JHU.

University of Louisville (UL)

Name:	Christina L. Kaufman, PhD (CK)
Project Role:	Collaborating PI
ORCID ID:	
Nearest person month worked:	1
Contribution to Project:	Dr. Kaufmann oversees all aspects of the project-related activities at UL.

University of California Los Angeles (UCLA)

Name:	Kodi Azari, MD, FACS (KA)
Project Role:	Collaborating PI
ORCID ID:	
Nearest person month worked:	0.2
Contribution to Project:	Dr. Azari oversees all aspects of the project-related activities at UCLA

University of Pennsylvania (UPenn)

Name:	L. Scott Levin, MD
Project Role:	Collaborating PI
ORCID ID:	0000-0001-9108-5182
Nearest person month worked:	0.2
Contribution to Project:	Dr. Levin oversees all aspects of the project-related activities at PM.
Name:	Annamarie Horan, PhD
Project Role:	Co-I
ORCID ID:	0000-0003-3000-5841
Nearest person month worked:	0.2
Name:	Mary Dooley, PhD
Project Role:	Co-I
ORCID ID:	0000-0002-0647-6187
Nearest person month worked:	0.2

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. Nothing to report.

COLLABORATIVE AWARDS:

QUAD CHARTS: See Appendix A

9. APPENDICES: See Appendix A for Quad Chart.

Appendix A: Quad Chart. Assessing the Comparative and Longitudinal Benefits of Vascularized Composite Allotransplantation of the Hand

Log Number:RT190094 Award Number: W81XWH-20-2-0061

PI: CAPT Scott M. Tintle Organization: Walter Reed National Military Medical Center Award Amount: $494,635

Specific Aims

Aim 1: Assess the benefits of upper extremity (UE) vascularized composite allotransplantation (VCA) across emotional, social, physical, and functional domains. (1a) Understand the relative value of UE VCA compared to other treatment options (e.g., prosthetics, reconstruction, osseointegration). (1b) Document how UE VCA affects social roles, interactions, and functioning, including sense of self and wholeness.

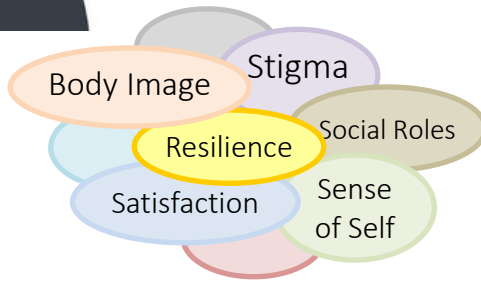
Aim 2: Explore how psychosocial functioning and QOL change over time for UE VCA recipients.

Aim 3: Develop a consensus set of psychosocial and QOL outcome variables that can be assessed longitudinally across VCA clinical centers.

Approach

These aims will be accomplished by using state-of-the-art qualitative and quantitative methods, employing both open-ended interviews and population-specific patient-reported outcomes (PRO) measurement items to assess quality of life (QOL) in four clinical groups: individuals who have undergone hand transplantation (n = 25), those with limb preservation or reconstruction (n = 25), traditional prosthesis users (n = 25, including myoelectric and body-powered), and those with osseointegrated prosthetics (n = 25).

Qualitative interviews will generate ***comparative*** and ***longitudinal*** information on psychosocial and QOL outcomes.



Results will lead to recommended **common data elements** for evaluating and monitoring outcomes across VCA clinical centers.

Accomplishments: During this quarter, we continued work on the regulatory and administrative documentation to launch the study. The study protocol has been approved by the University of Delaware IRB and HRPO, and regulatory and reliance agreement paperwork is either being prepared or is under review at all the partnering sites. Paperwork for a CRADA with Walter Reed was initiated, with the goal of engaging all sites.

Timeline and Cost

Activities and Milestones	Year 1	Year 2	Year 3	NCE
Finalize study procedures and protocol				
Coordinate regulatory and administrative approvals				
Develop data collection platform and finalize interview procedures				
Recruit participants (n = 100) and complete baseline interviews				
Analyze qualitative baseline interview data and summarize Aim 1 results				
Develop longitudinal data collection platform and interview procedures				
Re-contact participants (n = 100) and complete longitudinal interviews				
Analyze qualitative longitudinal interviews and summarize Aim 2 results				
Develop proposed set of consensus outcomes measures				
Share recommendations with VCA collaborators and gather feedback				
Revise recommendations based on feedback				
Summarize Aim 3 recommendations and disseminate to VCA clinical sites				
Estimated Budget ($K)	$	$	$	n/a

Goals/Milestones

Year 1 Goals: Regulatory and Administrative Approvals

- ☑ Milestone: IRB and HRPO approval obtained at University of Delaware
- ☑ Milestone: IRB and HRPO approval obtained at Walter Reed
- ☐ Milestone: IRB, HRPO & administrative approvals obtained at participating sites

Year 2 Goals: Complete Baseline Interviews & Analyze Aim 1 Results

- ☐ Milestone: Participant interviews (n = 100) completed
- ☐ Milestone: Analyses for Aim 1 completed

Year 3 Goals: Complete Longitudinal Interviews & Analyze Aim 2 Results; Develop and Finalize Recommended Common Data Elements

- ☐ Milestone: Longitudinal interviews (n = 100) completed
- ☐ Milestone: Analyses for Aim 2 completed
- ☐ Milestone: Final recommendations summarized and shared

Comments/Challenges/Issues/Concerns

Some regulatory delays due to pandemic and gaining site reliance for unified IRB. Expenditures delayed to assure funds are available to accomplish all goals.

Budget Expenditure to Date Projected Expenditure: **$**
Actual Expenditure: **$ 360,662.41**