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

PRINCIPAL INVESTIGATOR: David Tulsky, PhD

CONTRACTING ORGANIZATION: University of Delaware, Newark, DE

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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. To date, a comprehensive multi-site study protocol has been reviewed and approved by the University of Delaware IRB and by HRPO. We have worked with participating sites to establish reliance agreements for single IRB review. Paperwork for a CRADA with Walter Reed was initiated, with the goal of engaging all sites.

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	90
Subtask 1.4: Coordinate IRB protocol submissions at other recruitment sites	75
Subtask 1.5: Coordinate protocol submission to HRPO at UD	100
Subtask 1.6: Coordinate protocol submission to HRPO at WR	0
Subtask 1.7: Coordinate protocol submission to HRPO at other sites, as necessary	0
Subtask 1.8: Coordinate administrative approvals (e.g., Data Sharing Agreements) among all sites, as necessary	50

Statement of Work – Tasks and Subtasks	% Complete
Major Task 2: Conduct Baseline Interviews with Participants (n = 100)	
Subtask 2.1: Develop data collection platform (i.e., REDCap) and finalize interview procedures	0
Subtask 2.2: Recruit and screen participants	0
Subtask 2.3: Enroll and interview participants	0
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 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 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.

In year 2, we obtained approval of our multi-site protocol by HRPO. We have 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 have been completed, including UD IRB approval, and the formal reliance agreement awaits final signature at WR. At BWH, cede approval was submitted and approval at the site is expected at the start of year 3. MGH, JH, and Penn have each received local approval for reliance agreements; paperwork submission from them to UD IRB is pending. UL and UCLA reliance reviews are pending. In addition, staff at WR have begun 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 have been established with participating sites. **Since we have not yet received full regulatory approval at any site, no grant funds have been used during this period, nor have any grant funds been spent to date. However, now that regulatory approvals are imminent at many sites, we will begin using grant funds in year 3.**

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

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

In year 3 of this project, we will obtain all remaining IRB and HRPO approvals for recruiting patient participants from the involved sites, finalize site-specific agreements for data sharing and other administrative concerns, develop the data collection procedures and platform, train data collectors, and initiate the patient participant interviews.

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 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 seven sites, all of which have idiosyncratic review and procedures for participant safeguards. To address this, we have delayed expenditures to assure funds are available to accomplish all project goals. We are working closely with representatives from all sites to establish single IRB reliance agreements as well as a CRADA that will cover all sites. In addition, we are exploring additional partnerships with upper extremity transplant centers with English-speaking participants, to help ensure we meet enrollment targets. For example, we have had initial discussions with Leeds Teaching Hospitals in the United Kingdom, and they have expressed interest in potentially joining our consortium. The Leeds site has completed upper extremity transplants on eight patients, so their potential inclusion would meaningfully augment the participant pool.

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.

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

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 (WR)

Name:	**CDR Scott Tintle, MD**
Project Role:	Initiating PI at WR
ORCID ID:	0000-0003-0887-7600
Nearest person month worked:	1
Contribution to project:	CDR Tintle oversaw all aspects of the project-related activities, including teleconferences and initial planning activities.

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:	Dr. Dearth participated in project coordination activities.

Name:	**Toby Perkins**
Project Role:	Regulatory at WR
ORCID ID:	none
Nearest person month worked:	1
Contribution to project:	Ms. Perkins has been working on the IRB/CRADA/DSA.

University of Delaware (UD)

Name:	**David Tulsky, PhD**
Project Role:	Collaborating PI at UD
ORCID ID:	0000-0002-4335-4509
Nearest person month worked:	1
Contribution to Project:	Dr. Tulsky oversaw all aspects of the project-related activities at UD, including planning teleconferences and creation of IRB protocol at UD.

Name:	**Jerry Slotkin, PhD**
Project Role:	Co-Investigator at UD
ORCID ID:	0000-0001-8199-3056
Nearest person month worked:	1
Contribution to Project:	Dr. Slotkin participated in planning teleconferences, UD IRB protocol creation, and CRADA development.

Name:	**Callie Tyner, PhD**
Project Role:	Co-Investigator at UD
ORCID ID:	0000-0003-2945-392X

Nearest person month worked: 1
Contribution to Project: Dr. Tyner participated in planning teleconferences, led the UD IRB protocol development, and assisted with CRADA development.

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

University of Delaware (UD)

David Tulsky, Ph.D.

New funding:

1. Title: iManage-Sexual Wellness: Development of a symptom-monitoring/self-management program to enhance sexual wellness after SCI and TBI
   Funding Agency: National Institute on Disability, Independent Living, and Rehabilitation Research
   Project dates: 2/4/2022-08/31/2025
   Effort: 1.2 academic, 0.66 summer
   Description: The goal of this five-year project is to create and evaluate a web-based symptom-monitoring/self-management system to improve sexual wellness in individuals with SCI or TBI.
   Overlap: none

Previous funding:

- Online Symptom-Monitoring/Self-Management for Pandemic-Related Emotional Distress (ACCEL), ended 06/30/2022

Jerry Slotkin, Ph.D.

New funding:

1. Title: iManage-Sexual Wellness: Development of a symptom-monitoring/self-management program to enhance sexual wellness after SCI and TBI
   Funding Agency: National Institute on Disability, Independent Living, and Rehabilitation Research
   Project dates: 2/4/2022-08/31/2025
   Effort: 0.48 calendar
   Description: The goal of this five-year project is to create and evaluate a web-based symptom-monitoring/self-management system to improve sexual wellness in individuals with SCI or TBI.
   Overlap: none
2. Title: ARMADA: Advancing Reliable Measurement in Alzheimer's Disease and cognitive Aging
   Funding Agency: Northwestern University/National Institutes of Health
   Project dates: 5/1/2022-12/31/2022
   Effort: 0.70 calendar
   Description: Cognitive decline and dementia due to Alzheimer's Disease, both associated with advancing age over 65, are increasing in the US due to the reduction of other illnesses that, in the past, limited life expectancy. This project will provide a brief, comprehensive assessment tool (in English and Spanish versions), applicable to diverse populations, to screen for a decline in cognitive health and associated neurological

functions. The burden of age-related cognitive decline and dementia on older adults and the health care system make their early identification a critical public health goal in order to pave the way for prevention trials.
Overlap: none

Previous funding:

- Online Symptom-Monitoring/Self-Management for Pandemic-Related Emotional Distress (ACCEL), ended 06/30/2022

Callie Tyner, Ph.D.

New funding:

1. Title: iManage-Sexual Wellness: Development of a symptom-monitoring/self-management program to enhance sexual wellness after SCI and TBI
   Funding Agency: National Institute on Disability, Independent Living, and Rehabilitation Research
   Project dates: 2/4/2022-08/31/2025
   Effort: 0.48 calendar
   Description: The goal of this five-year project is to create and evaluate a web-based symptom-monitoring/self-management system to improve sexual wellness in individuals with SCI or TBI.
   Overlap: none

Previous funding:

Nothing to report

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

Collaborative Awards

n/a

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: RT190094P1; Award Number: W81XWH-20-2-0062

PI: David Tulsky, PhD **Organization:** University of Delaware **Award Amount:** $1,000,152

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.

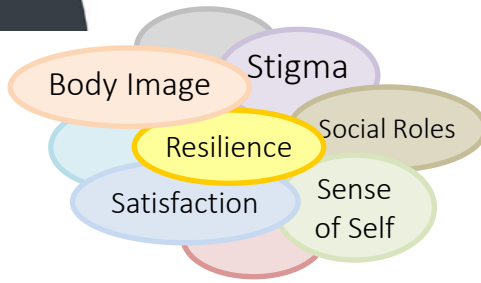
Aim 3: Develop a consensus set of psychosocial and QOL outcome variables that can be assessed longitudinally across VCA clinical centers.

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 Year 2, we worked on the regulatory and administrative documentation to launch the study. The study protocol was approved by HRPO. We have worked with participating sites to establish reliance agreements. 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
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 outcome 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	*$280k*	*$384k*	*$336k*

Updated: 21-Oct-2022

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: **$663,634**
Actual Expenditure: **$0**