FY20 Reconstructive Transplant Research Program Clinical Network Award
Question and Answer Session
29 October 2020

The Reconstructive Transplant Research Program (RTRP) held a Question and Answer (Q&A) Session on 29 October 2020 to address questions from the research community regarding a new award mechanism, the Clinical Network Award (https://cdmrp.army.mil/funding/pa/FY20-RTRP-CNA.pdf). The session was advertised via an Electronic Biomedical Research Application Portal (eBRAP) email blast and grants.gov. Participants were asked to announce their plans to attend the session by sending an email RSVP to the RTRP mailbox at usarmy.detrick.medcom-cdmrp.mbx.cdmrp-rtrp@mail.mil. Instructions for participating in the session were then sent to respondents via email. The meeting was supported by Leidos, using the Adobe Connect platform. A summary of the meeting is detailed below.

A brief overview of the FY20 RTRP Clinical Network Award was presented by Dr. Trish Henry, the RTRP Program Manager (Appendix 1). The intent of this award mechanism is to support the establishment of a major multi-institutional network of Vascularized Composite Allotransplantation (VCA) Centers and associated collaborators for the purpose of standardizing clinical protocols and Standard Operating Procedures (SOPs) for face and hand transplantation and assessing those protocols and SOPs in multi-institutional clinical trials (one for face transplantation and one for hand transplantation). The RTRP would like to bring together investigators from as many VCA Centers as possible for both face and hand transplantation to establish a consensus in the field of reconstructive transplantation for these face and hand transplantation protocols. The RTRP recognizes that such a consensus is a necessary first step to advancing face and hand transplantation from experimental status to that of a viable choice with the potential for reimbursement under health insurance policies. Thus, this award mechanism has a narrow focus and is not open to other research questions.

The applicant, who is proposing to serve as the Coordinating Center for the Clinical Network, must address the standardization, assessment, and validation of protocols and/or SOPs for all of the following Focus Areas for both face and hand transplantation:

- Patient inclusion/exclusion criteria
- Patient education
- Surgical procedures
- Immunosuppression and/or immune regulation
- Outcome metrics
- Quality of life measures
- Rehabilitation
- Patient reporting (e.g., registry)

It is anticipated that a single award will be made to the Coordinating Center. This will be a two-phased approach. The first phase will include establishment of the Clinical Network via sub-awards to VCA Centers and other collaborators, development of standardized protocols and SOPs, and preparation for the resulting clinical trials in face and hand transplantation. The period of performance for Phase I is 2 years, with total costs of up to a maximum of $3 million (M). Assuming that all of the objectives in Phase

I are achieved and the RTRP has available funding (anticipated in FY22), Phase II can be executed. The second phase will include conducting two multi-institutional clinical trials (one for face transplantation and one for hand transplantation). The period of performance of Phase II is 4 years, with total costs of up to a maximum of $10M. The RTRP Clinical Network Steering Committee will provide oversight of all aspects of the Clinical Network and will provide guidance at critical junctures. The Coordinating Center and Network Site Principal Investigators are required to present updates to the RTRP Clinical Network Steering Committee at annual In Progress Review (IPR) meetings.

There are five key objectives for Phase I:

1. **Establish the Clinical Network.** The Coordinating Center will work with the RTRP Steering Committee to invite VCA Centers and other collaborators into the Clinical Network as sub-awards to serve as Network Sites. Applicants should not be forming Network collaborations at the time of application submission. The RTRP is looking for the strongest applicant to become the Coordinating Center (i.e., the one that will be best able to facilitate achievement of the Clinical Network's objectives). The Clinical Network will be built around the Coordinating Center after the award has been made. The Clinical Network will be representative of both face and hand transplantation and include expertise across all eight Focus Areas.
2. **Develop standardized protocols and SOPs for face and hand transplantation.** The Coordinating Center will develop a framework and collaborative environment for Network Sites to work as equal partners. Personnel across the Network Sites will work together to develop the standardized protocols and SOPs for face and hand transplantation across all eight Focus Areas.
3. **Develop two clinical trial applications.** The standardized protocols and SOPs will then be used to develop one clinical trial application for face transplantation and one clinical trial application for hand transplantation.
4. **External scientific review of clinical trial applications.** The Coordinating Center will fund and coordinate an external scientific review of the two clinical trial applications and submit the results to the RTRP Clinical Network Steering Committee for review.
5. **Obtain all necessary regulatory clearances and/or approvals.** If aspects of the standardized protocols require Food and Drug Administration (FDA) clearance, this step must be completed during Phase I. In addition, all Institutional Review Board (IRB) and Department of Defense Office of Research Protections (ORP) Human Research Protection Office (HRPO) approvals must also be obtained during Phase I.

The Phase II option may be exercised pending successful completion of Phase I objectives and availability of funds. Thus, if the RTRP receives funds in FY22 and all Phase I objectives are successfully completed, it is anticipated that the Phase II option would be exercised. There is one main objective for Phase II, which is to conduct one clinical trial in face transplantation and one clinical trial in hand transplantation. The Network Sites that have VCA Centers will serve as enrollment sites for the clinical trials. The clinical trials must open for enrollment within 2 months after the start of Phase II. Since all regulatory clearances and approvals will have been obtained during Phase I, this is not expected to be a problem.

The Coordinating Center will serve as the Clinical Network information and planning nexus, providing administrative, operational, and data management support services to implement Clinical Network activities in a timely manner. Key requirements and responsibilities of the Coordinating Center are listed on pages 5–8 of the Program Announcement. The Network Sites are to serve as equal partners in the Clinical Network and are responsible for working collaboratively with the Coordinating Center and other Network Sites to meet the objectives of the Clinical Network. Key requirements and responsibilities of the Network Sites are listed on pages 8–9 of the Program Announcement.

The following questions were addressed during the session.

Will any unused funding award in Phase I roll over for use in Phase II?

The Phase II Option, if exercised, will be executed as a modification of the original award agreement. Any funds not used during Phase I would remain available for use during Phase II.

For the SOW, should applicants map a plan for Phase II?

The Program Announcement indicates that applicants should delineate the aims and tasks for both Phase I and II. The RTRP understands that applicants will not know exactly what Phase II will look like without the clinical protocols, so details are not expected; however, applicants should still list general tasks that can be anticipated for the clinical trials.

How is the strongest applicant being defined?

The strongest applicant will be determined based on the peer and programmatic review criteria listed in the Program Announcement. Peer review criteria are listed starting on page 32, and applicants will find that these criteria correlate very well with the requirements listed for the project narrative (beginning on page 18). These criteria include the following categories: Network Development Plan, Personnel and Resources, Network Coordination, Protocol and SOP Development, Clinical Trial Development, and Clinical Trial Management.

Does the extent of the criteria for evaluation extend to just post-recovery or does it go into the phases of immediate triage? (In other words, are proposals to be considered for both the evacuation stage after battlefield explosion, as well as infection response thereafter? Infectious disease tissue loss can make transplants more challenging.)

VCA is a procedure that takes place well after the acute period of injury and well after any battlefield care that may take place. This funding opportunity is focused specifically on establishing a standard process for face and hand transplantation and is not open to research during the acute or sub-acute phase of injury care.

Is the time frame not to exceed the period of performance, meaning 24 months? (Exactly how is the 24 months decided?)

The period of performance for Phase I is 2 years, but it is possible that a no-cost extension will be needed to complete all of the Phase I objectives. Thus, Phase I could extend beyond 24 months, but Phase II would not go into effect until all of the Phase I objectives are completed.

Is the focus on clinical trial outcomes or are novel treatments/monitoring encouraged?

The focus is to develop standardized protocols that VCA Centers can agree upon to be the standard for the field. If everyone comes together and agrees that a novel treatment should be the standard, then that can be part of an applicant's protocol. The goal is to move VCA out of the experimental treatment realm and into something that can be considered standard of care. The RTRP is looking for everyone to come together and agree on the baseline standard protocol.

Should the application for the Coordinating Center include detailed proposals for the focus of the two clinical trials in Phase II?

No. The clinical trials to be proposed for Phase II will be developed during Phase I of the award. When the Clinical Network is assembled and all Network Sites agree upon what is to be considered standard, the clinical trial applications will then be developed based on those set standards.

How often will project benchmarks be reviewed? May Phase I and II run in parallel?

No. Phase I must be completed before Phase II can begin. There are a few different ways that Clinical Network progress will be reviewed. The RTRP will hold annual IPRs, ideally in person in front of the RTRP Clinical Network Steering Committee; however, depending on the status of COVID-19 protocols, the meetings may be virtual. Quarterly and annual reports also will be submitted by the Coordinating Center for review by the RTRP staff.

Are face-to-face meetings at months 6 and 18 in addition to the annual in-person meetings?

The Clinical Network review meetings are separate from the IPR meetings and are to be hosted by the Coordinating Center as a way to get all of the sites together to discuss their progress as a group. The RTRP Steering Committee is to be invited, but the meetings will be organized by the Coordinating Center. The intent is to get the Coordinating Center and Network Sites together to do a self-assessment of where they are and what steps need to be taken next to accomplish the objectives. The RTRP recommends months 6 and 18 because that is when the program thinks it might be most helpful.

Will the annual review meetings come out of the Coordinating Center budget?
Yes. The Coordinating Center needs to fund the meeting from their budget. Note that these meetings are for Phase I of the Clinical Network.

Can "Compassionate Use" be included in an Investigational New Drug (IND) application status?

If the Clinical Network decides to include the new drug as part of the standardized protocols, then the FDA will need to provide a clearance to proceed with the clinical trial. If "Compassionate Use" is included as part of the IND application and is approved by the IRB and HRPO, then it should be fine for the clinical trial.

Will civilian reviewers be invited to participate in the grant reviews?

The Congressionally Directed Medical Research Programs (CDMRP) has a two-tier review, the first of which is the peer review (i.e., scientific review), which will be conducted by General Dynamics Information Technology. They will put together panels of experts to review these applications. Many of those recruited to serve on the panel will be from the civilian sector, such as universities and hospitals. Occasionally, there may also be military representation on the peer review panels. The second tier of review, programmatic review, is conducted by Leidos. The list of Programmatic Panel members is posted on the RTRP web page at https://cdmrp.army.mil/rcrp/panels/panels20. Many of these panelists are also from the civilian sector.

If a trial is proposed for Phase II, can it be modified based on the results of Phase I?

An application that is submitted now will not include proposals for clinical trials. Clinical trial proposals will be developed during the Phase I award and will be developed by the Clinical Network to assess the standardized protocols and SOPs that were developed during Phase I.

Additional questions can be sent to the RTRP mailbox at usarmy.detrick.medcom-cdmrp.mbx.cdmrp-rtrp@mail.mil.

Appendix 1

Congressionally Directed Medical Research Programs,

Reconstructive Transplant Research Program (RTRP)
Fiscal Year 2020 (FY20)
Clinical Network Award
Q & A Session

CUTTING EDGE RESEARCH

Trish Henry, Ph.D.
Program Manager, RTRP






CDMRP
Department of Defense

WHO is the CDMRP?

- Department of Defense
  - Department of the Army
    - Army Futures Command
      - U.S. Army Medical Research and Development Command (USAMRDC)
        - Congressionally Directed Medical Research Programs

RTRP Vision and Mission

Vision

Reconstructive transplant: an accessible reality and viable choice

Mission

Expand reconstructive options for catastrophically injured Service members, Veterans, and American civilians by developing a standardized conduct of VCA procedures

Clinical Network Award

Intent

- To support the establishment of a major multi-institutional network of VCA Centers and associated collaborators for the purpose of standardizing clinical protocols and SOPs for face and hand transplantation, and assessing those protocols and SOPs in multi-institutional clinical trials

- To bring together investigators from as many VCA Centers for both face and hand transplantation as possible to establish a consensus in the field of reconstructive transplantation for these face and hand transplantation protocols

FY20 Clinical Network Award Focus Areas

To meet the intent of the FY20 RTRP Clinical Network Award mechanism, applicants must address the standardization, assessment, and validation of protocols and/or standard operating procedures (SOPs) for all of the following focus areas for both face and hand transplantation.

- **Patient inclusion/exclusion criteria**
- **Patient education**
- **Surgical procedures**
- **Immunosuppression and/or immunoregulation**
- **Outcome metrics**
- **Quality of life measures**
- **Rehabilitation**
- **Patient reporting (e.g., registry)**

Key Features

- **Single award to the Coordinating Center**
  - Applicant is proposing to serve as Coordinating Center for the Clinical Network
- **Two-phased approach**
  - **Phase I:** Establish Clinical Network, develop standardized protocols and SOPs, and prepare for resulting clinical trials in face and hand transplantation
  - **Phase II Option:** Conduct clinical trials (one face and one hand transplant trial)
- **Period of Performance**
  - Phase I: 2 years
  - Phase II: 4 years
- **Maximum Total Costs**
  - Phase I: $3 M
  - Phase II Option: $10 M
- **Oversight by the RTRP Clinical Network Steering Committee**
  - Will provide oversight of all aspects of the Clinical Network
  - Will provide guidance at critical junctures
  - In Progress Reviews: Coordinating Center and Network Site PIs are required to present updates to the Steering Committee at annual IPR meetings

Phase I Objectives

- **Establish Clinical Network**
  - Coordinating Center will work with the RTRP Steering Committee to invite VCA Centers and other collaborators into the Clinical Network as subawards to serve as Network Sites (i.e., Network Sites are not to be selected prior to award)
  - Clinical Network will be representative of both face and hand transplantation, and include expertise across all 8 Focus Areas
- **Develop standardized protocols and SOPs for face and hand transplantation**
  - Coordinating Center will develop a framework and collaborative environment for Network Sites to work as equal partners
- **Develop 2 clinical trial applications**
  - One clinical trial for face transplant and one for hand transplant
- **External Scientific Review of the 2 clinical trial applications**
  - Coordinating Center will fund and coordinate an external scientific review, and submit the results to the RTRP Clinical Network Steering Committee
- **Obtain all necessary regulatory clearances and/or approvals**
  - To include FDA (if applicable), IRB, and HRPO approvals

Phase II Option

The option for Phase II may be exercised pending successful completion of Phase I objectives and availability of funds.

Objective:

- **Conduct one clinical trial in face transplantation, and one clinical trial in hand transplantation**
  - The clinical trials are intended to assess and validate the standardized protocols developed in Phase I
  - Network Sites with VCA Centers will serve as enrollment sites for at least one of the clinical trials, depending on specialty in face and/or hand transplantation
  - The clinical trials must open for enrollment within 2 months after the start of Phase II

Coordinating Center

- **Will serve as the Clinical Network information and planning nexus, providing administrative, operational, and data management support services to implement Clinical Network activities in a timely manner**
- **Responsibilities:**
  - Develop and maintain the Clinical Network organizational structure
  - Provide day-to-day management of the Clinical Network
  - Establish procedures to ensure funding for Network Sites
  - Facilitate the necessary agreements between all Network Sites to ensure seamless collaboration
  - Develop and manage a communications plan
  - Establish and maintain an intellectual and material property plan
  - Manage real or perceived conflicts of interest
  - Facilitate a collaborative research environment
  - Establish a fair and equitable process for protocol and SOP development
  - Provide a Clinical Research Manager
  - (See full list in Program Announcement, pp. 6-8)

Network Sites

- **Will be invited into the Clinical Network as subawards after the Coordinating Center has been awarded**
- **Network Sites are to serve as equal partners in the Clinical network and are responsible for working collaboratively with the Coordinating Center and the other Network Sites to meet the objectives of the Clinical Network**
- **Responsibilities:**
  - Work with the Coordinating Center to complete all necessary agreements
  - Participate and work collaboratively to develop standardized protocols in face and/or hand transplantation
  - Participate in, comply with, and/or implement the Coordinating Center's established procedures for the Clinical Network
  - Provide a Clinical Research Coordinator
  - (See full list in Program Announcement, pp. 8-9)

Questions

- **Will any unused funding awarded in Phase I rollover for use in Phase II?**
  - The Phase II Option, if exercised, will be executed as a modification of the original award. Any funds not used during Phase I will remain available for use during Phase II.

Thank you for your service!

◆CDMRP

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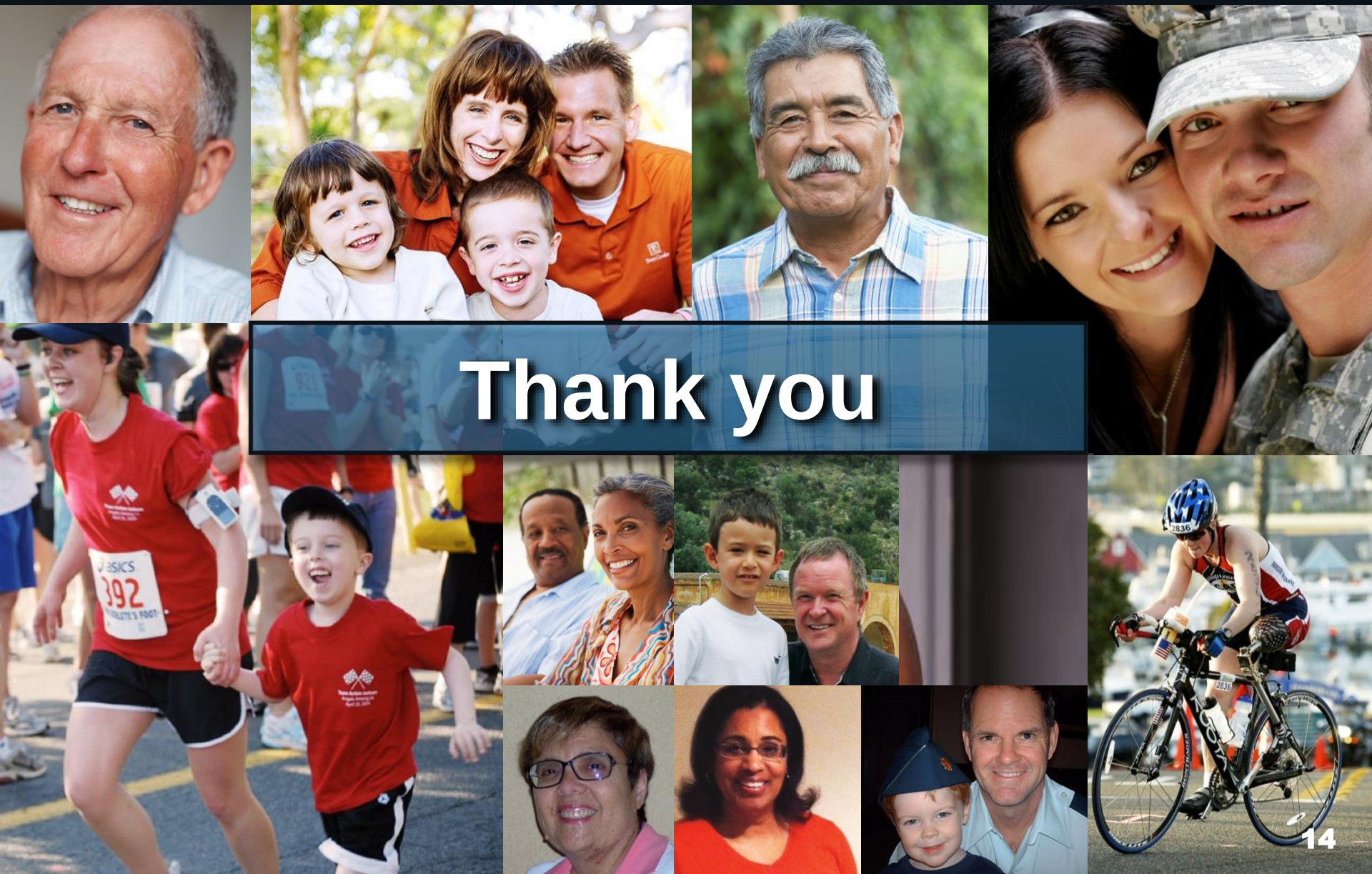
For your Service and Participation



Thank you