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TITLE: Multi-site Confirmatory Efficacy Treatment Trial of Combat-Related PTSD

PRINCIPAL INVESTIGATOR: John Hart, Jr., MD

CONTRACTING ORGANIZATION: The University of Texas at Dallas, Richardson, TX

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The University of Texas at Dallas
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Richardson, TX 75080

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The present study is a multisite trial with randomization of 330 OEF/OIF/OND veterans with combat related post-traumatic stress disorder (PTSD) to one of three treatment arms – 1 Hz repetitive transcranial magnetic stimulation (rTMS) to the right frontal dorsal lateral prefrontal cortex (rDLPFC) alone, 1 Hz rDLPFC rTMS + Cognitive Processing Therapy (CPT), or sham rTMS + CPT to determine which of these treatments is most effective for reducing PTSD symptoms, as measured by the CAPS-5, and PCL-5.

We have established the research team, laboratory setting, maintained approval of all regulatory documents for all performance locations for the study, and established recruiting procedures. We have recruited 214 subjects for the study and enrolled (randomized) 59 out of 330 subjects in the baseline testing and treatment phase of the study.

15. SUBJECT TERMS

Post-traumatic Stress Disorder (PTSD), Cognitive Processing Therapy (CPT), repetitive magnetic transcranial stimulation (rTMS)

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1. INTRODUCTION:

The present study is a multisite trial with randomization of 330 OEF/OIF/OND veterans with combat related post-traumatic stress disorder (PTSD) to one of three treatment arms – 1 Hz repetitive transcranial magnetic stimulation (rTMS) to the right frontal dorsal lateral prefrontal cortex (rDLPFC) alone, 1 Hz rDLPFC rTMS + Cognitive Processing Therapy (CPT), or sham rTMS + CPT to determine which of these treatments is most effective for reducing PTSD symptoms, as measured by the CAPS-5 and PCL-5.

2. KEYWORDS:

Post-traumatic stress disorder (PTSD), Cognitive Processing Therapy (CPT), repetitive magnetic transcranial stimulation (rTMS)

3. ACCOMPLISHMENTS:

What were the major goals of the project?

	Timeline Months	Status	% Complete
PreStudy Tasks		Complete	100
Aim 1: Conduct multisite trial with randomization of 330 Veterans with combat related PTSD to one of three treatment arms			
Task 1: Contact, recruit and screen patients for study enrollment. Screen 505 participants	4-48	In process	34%
Task 2: Perform pre-treatment neuropsychiatric assessments for 330	4-48	In process	18%
Task 3: Perform active rTMS/CPT, sham rTMS/CPT, or rTMS alone for 330	4-48	In process	15%
Task 4: Perform post-treatment neuropsychiatric assessment at 1 mo, 6 mo, and 12 mo after last treatment for 231	8-54	In process	14%
Task 5: Perform longitudinal analysis on neuropsychiatric measures of treatment efficacy	37-60	Not yet initiated	-
Task 6: Prepare and submit manuscript on treatment efficacy	49-60	Not yet initiated	-
Aim 2: Use functional MRI and Event Related Potential to better understand brain changes that occur upon treatment of PTSD			
Task 1: Perform pre-treatment ERPS for threatening stimuli for 330	4-48	In process	18%
Task 2: Perform pre-treatment fMRIs for threatening stimuli for 255	4-48	In process	12%
Task 3: Perform post-treatment ERP for threatening stimuli at 6 and 12 mo for 231	8-54	In process	6%; 3%
Task 4: Perform post-treatment fMRI for threatening stimuli at 6 and 12 mo for 179	8-54	In process	7%; 2%
Task 5: Perform longitudinal analysis of ERP measures of treatment efficacy	37-60	Not yet initiated	-
Task 6: Prepare longitudinal analysis of fMRI measures of treatment efficacy	37-60	Not yet initiated	-
Task 7: Prepare and submit manuscripts on ERP measures	49-60	Not yet initiated	-
Task 8: Prepare and submit manuscripts on fMRI measures	49-60	Not yet initiated	-

What was accomplished under these goals?

We have maintained approval of regulatory requirements for all performance sites and continue to revise recruiting procedures to increase numbers. The study is live on ClinicalTrials.gov with a Certificate of Confidentiality from NIH. The Fidelity Monitor has reviewed CPT sessions and the Data Safety Monitoring Board meets yearly.

We continue to grow our recruiting network and social media presence across sites. This year, the FSU site contracted with Local IQ through July 31, 2022 to implement ad services on Facebook and sponsored search ads. The UTD site began a similar strategy in April. Instead of working with a third party, UTD worked directly with Facebook Ad Services to promote the study on Facebook and Instagram.

The Steven A. Cohen Military Family Clinic at Metrocare site is continuing to have the research assistant prescreen all incoming clients and coordinating with clinicians to screen interested candidates. Metrocare is continuing to track why potential candidates may not be interested in the study, through their clinicians, in hopes they may identify and reduce barriers to participation.

The COVID-19 pandemic greatly impacted recruitment for this study. But this past year, we have seen an increase of 63% in recruitment and 103% in randomization with the Facebook marketing campaign, reduction of restrictions, and willingness of subjects to participate in "in-person studies". Across sites, we have recruited 214 subjects and randomized 59 subjects. Of the 59 randomized, 32 completed treatment phase and 12 completed follow up phase with 11 withdrawn during treatment and 3 lost during follow up. The withdrawal rate is 18.6% which is less than the 30% anticipated indicating that we could meet statistical validity with fewer enrolled.

PROTOCOL (1 of 1 total):

Protocol [HRPO Assigned Number]: E00131.1

Title: Multi-site confirmatory efficacy treatment trial of combat-related PTSD

Target required and approved for clinical significance: Enroll 330 with expectation of 231 (estimate of 30% possible attrition) for the final outcome measures

SUBMITTED TO AND APPROVED BY:

- 18 April 2019 – DoD HRPO approval of protocol
- 1 July 2022 – UT Southwestern acceptance of continuing review for all sites
- 10 August 2022 – DoD OHRO acceptance of continuing review for all sites

Number of subjects recruited/original planned target: 214/505
Number of subjects screened/original planned target: 172/505
Number of patients enrolled/original planned target: 59/330
Number of patients completed/original planned target: 12/231

No adverse event/unanticipated problems to report.

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?

Recruiting efforts are a priority. All three treatment sites continue to work on minimizing the pandemic's impact while ensuring the health and safety of their staff and participants. The sites are in regular contact with each other, sharing best practices, and leveraging resources.

UTD will continue its Facebook ad strategy. A new staff member was hired in July to meet the needs of the study, and a paid student intern was assigned to conduct initial screening of Facebook leads. In August, UTD started the third run of focused advertisement and received 86 leads within 3 weeks. UTD plans to continue to run ads on Facebook and fine tune the strategy to effectively reach potential participants. The Outreach Coordinator will continue to attend live recruitment events, visit VSOs in the area, and collaborate with the VA.

In August 2022, FSU will employ a similar strategy as UTD and handle Facebook Ad Services in-house. It expects to increase recruitment numbers as the ad service should reach a greater number of people on multiple platforms.

In the upcoming year, Metrocare plans to do more in person outreach events with their research assistant and outreach director to share the study with people who are not current clients of the clinic. It will also conduct more paid social media ads and use its monthly newsletter to reach out to past and current clients who may be interested in the study.

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?

We have made presentations to various agencies about our project and post-traumatic stress disorder to create awareness of both.

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

The Covid-19 pandemic continues to have a residual effect. Although enrollment numbers have increased numbers dramatically this past year, we cannot get back the nearly two years lost due to the pandemic. We are concerned with meeting our goals by the time funds expire in 2023.

We will continue to improve recruitment procedures, explore new options, and share ideas across sites. Current and proposed recruitment efforts are described in Section 3 above.

Due to schedule irregularities, FSU had some difficulty starting newly enrolled participants in the treatment phase. They are working to resolve this problem in several way, including but not limited to streamlining the scheduling process and including more in-depth conversations with participants on the possibility of a reluctance to move on to treatment after baseline.

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

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**

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?

John Hart, Jr., MD, Principal Investigator – No change

F. Andrew Kozel, MD, Co-Investigator, Site PI, Florida State University – No change

Michael Motes, PhD, Co-Investigator, UT Dallas – No change

Michael Kraut, MD, PhD, Co-Investigator, Johns Hopkins University – No change

John Burruss, MD, Co-Investigator, Site PI, Metrocare Services of Dallas – No change

Anushka Pai, MD, Co-Investigator, Site PI, UT Southwestern – No change

Elizabeth "Ellen" Morris, PhD, Project Coordinator/CPT Therapist, UT Dallas – No change

Jill Ritter, Research Manager, UT Dallas – No change

Kelsey Watson, Research Assistant, UT Dallas – No change

Tyler Rawlinson, Veteran Outreach Coordinator, UT Dallas – No change

Jared Brooks, Research Assistant, UT Dallas – No change

Elliot Ingram
Project Role: Research Assistant, UT Dallas
Nearest person month worked: 1 month
Contribution to Project: Sets up rTMS coil for administration, recruiting, screening, coordination and scheduling of visits, data entry, MRI and EEG acquisition and storage, and assists Dr. Morris

Vadym Zhyrov
Project Role: Research Assistant, UT Dallas
Nearest person month worked: started July 2022
Contribution to Project: Sets up rTMS coil for administration, recruiting, screening, coordination and scheduling of visits, data entry, MRI and EEG acquisition and storage, and assists Dr. Morris

Christina "Tina" Bass, M.S., LPC, CPT Therapist, UT Dallas – No change

Mary Turner, PhD, Independent Evaluator, UT Southwestern – No change

Kevin Johnson, PhD, RN, Co-I and TMS Administrator, Florida State University – No change

Isabelle Taylor, Research Program Manager, FSU Neuromodulation, Florida State University – No change

Jessica Greil-Burkhart, LCSW, CPT Therapist, Florida State University – No change

Megan Senda, Research Assistant, Florida State University – No change

Christina Riccardi, PhD, CPT Therapist, Florida State University – No change

Joseph Frascella, PhD, Backup unblinded study staff, Florida State University – No change

Sharon Liebrich, MSN, RN
Project Role: Additional backup unblinded study staff, Florida State University
Nearest person month worked: started June 2022
Contribution to Project: Unblinded study staff procedures including scheduling and coil setting

Mariah Jensen, CMA
Project Role: Research Assistant, Florida State University
Nearest person month worked: started July 2022
Contribution to Project: Blinded on the study. Assists in the administration of/administers rTMS treatment

Chelsea Fiduccia, PhD, Co-Investigator, Metrocare Services of Dallas – No change

Jordan Petry, Research Assistant, Metrocare Services of Dallas and UT Dallas – No change

Tanya Mac, Outreach Director, Metrocare Services of Dallas – No change

Nicolette Aguon, Intake Coordinator, Metrocare Services of Dallas – No change

Keah Odom, LCSW-S, CPT Therapist, Metrocare Services of Dallas – No change

Ashton Steele, PhD, CPT Therapist, Metrocare Services of Dallas – No change

John Bennett, MD, On-site Medical Director, Metrocare Services of Dallas – No change

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?

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: N/A

QUAD CHARTS: Attached

9. APPENDICES: Consort diagrams attached. One for each site.

Multi-site confirmatory efficacy treatment trial of combat-related PTSD

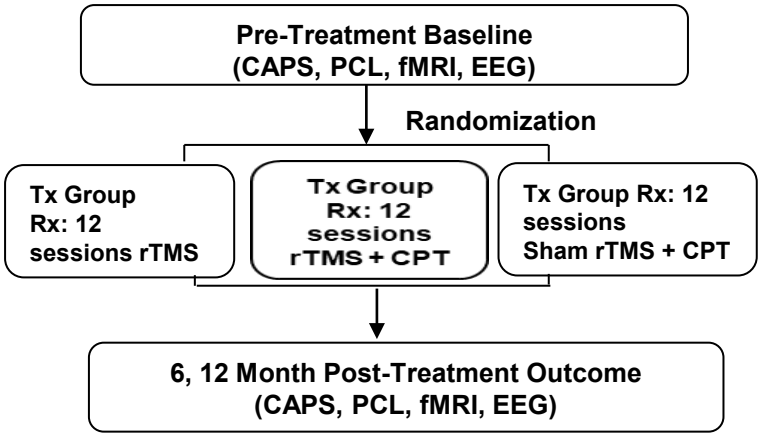
Log # BA160594; Award # W81XWH-18-1-0464

PI: John Hart, Jr., MD **Org:** The University of Texas at Dallas **Award Amount:** $7,359,925

Study/Product Aim(s)

- Aim 1: Conduct multisite trial with randomization of 330 OEF/OIF/OND veterans with combat-related PTSD to one of three treatment arms – 1 Hz rDLPFC rTMS alone, 1 Hz rDLPFC rTMS+CPT, or sham rTMS+CPT, and evaluations at 1 (neuropsychiatric behavioral measures and EEG only), 6 and 12 months post-treatment (neuropsychiatric, EEG, and fMRI measures).
- Aim 2: Use fMRI and ERP to better understand brain changes that occur upon treatment of PTSD symptoms.

Approach: Veterans with PTSD will be screened with neuropsychiatric questionnaires to establish eligibility. Then the CAPS-5, SCID, BDI-II, PCL-5, and neuropsychiatric self-report measures will be administered. Participants will then undergo ERP and MRI exams, including the fMRI visual threat task. They will then be randomly assigned (n=110 per group) to one of three treatment arms: 1) 12 sessions of 1 Hz rDLPFC for 30 min each immediately followed by a CPT session, 2) 12 sessions of 1 Hz rDLPFC for 30 mins without CPT, and 3) 12 sessions of sham rDLPFC rTMS each immediately followed by a CPT session. This study will be conducted at 3 sites: 1) Callier Center at UTD, 2) Metrocare of Dallas, and 3) Florida State University in Tallahassee, FL. One month following completion of the treatment sessions, participants will undergo a repeat of the above noted behavioral and EEG measures. At 6 and 12 months post-treatment, participants will again undergo these behavioral, ERP, and MRI including fMRI visual threat task.



Timeline and Cost

Activities / Yr	2019	2020	2021	2022	2023
1. Screening 505 veterans for PTSD diagnoses. 2. Acquiring pre-treatment neuropsychiatric baselines 3. Acquiring pre-treatment fMRI and EEG					
4. Treatment of 330 veterans					
5. Acquiring post-treatment 6. Analyzing data and disseminating findings					
Estimated Budget ($K)	$1.5M	$1.5M	$1.5M	$1.5M	$1.3M

Goals/Milestones

CY18 Goals

☐ Approval of regulatory documents

☐ Recruiting 30 subjects in treatment across sites

CY18-21 Goal

☐ Enrolling 330 subjects in the study

CY22 Goal

☐ Analyzing data

Comments/Challenges/Issues/Concerns

- Recruitment impacted by Covid-19 pandemic

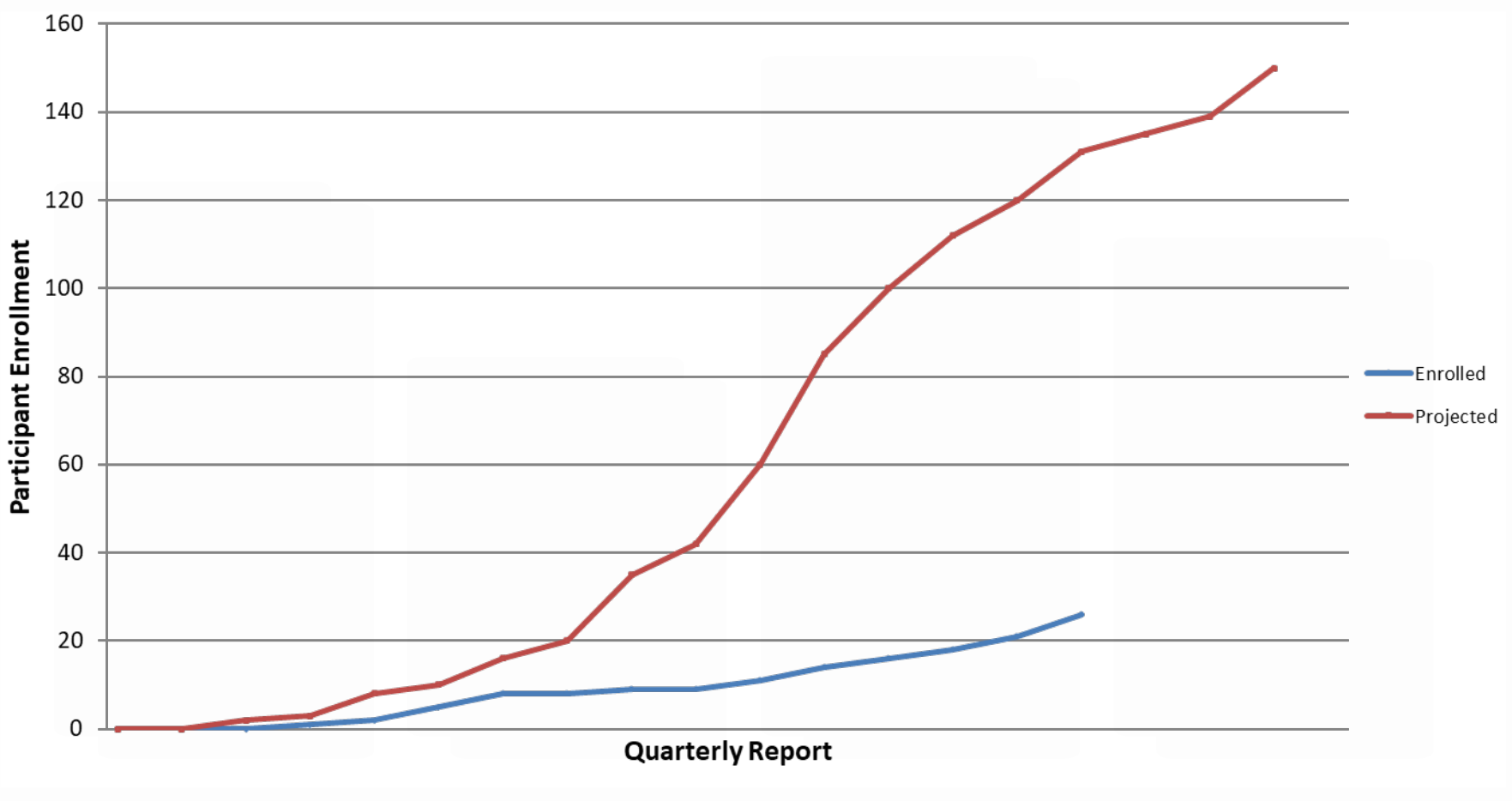
Budget Expenditure to Date

Projected Expenditure: $6,073,024

Actual Expenditure: $4,025,131

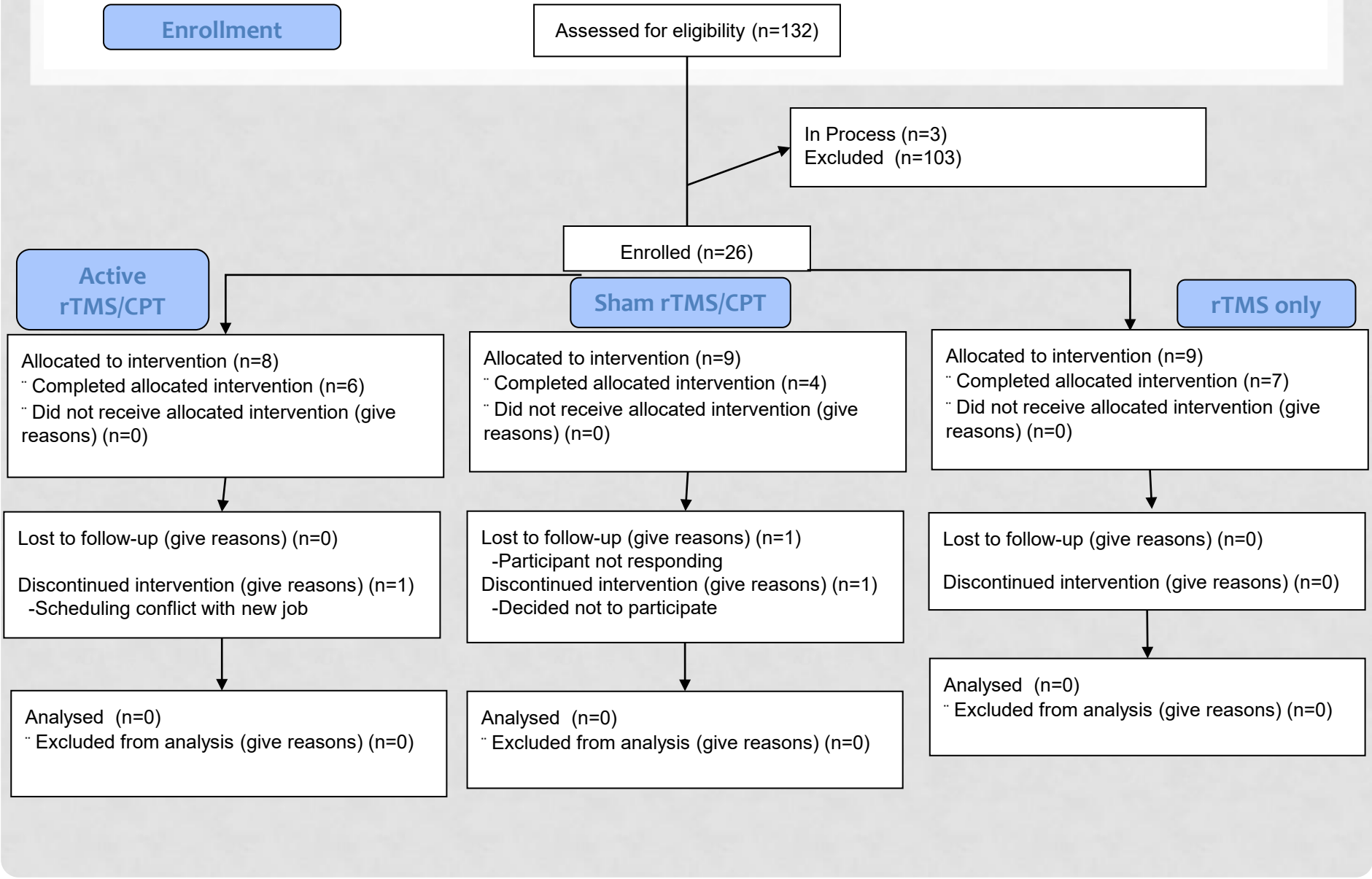
Updated: 16 August 2022

Recruitment and Retention – UT Dallas, Dallas, TX

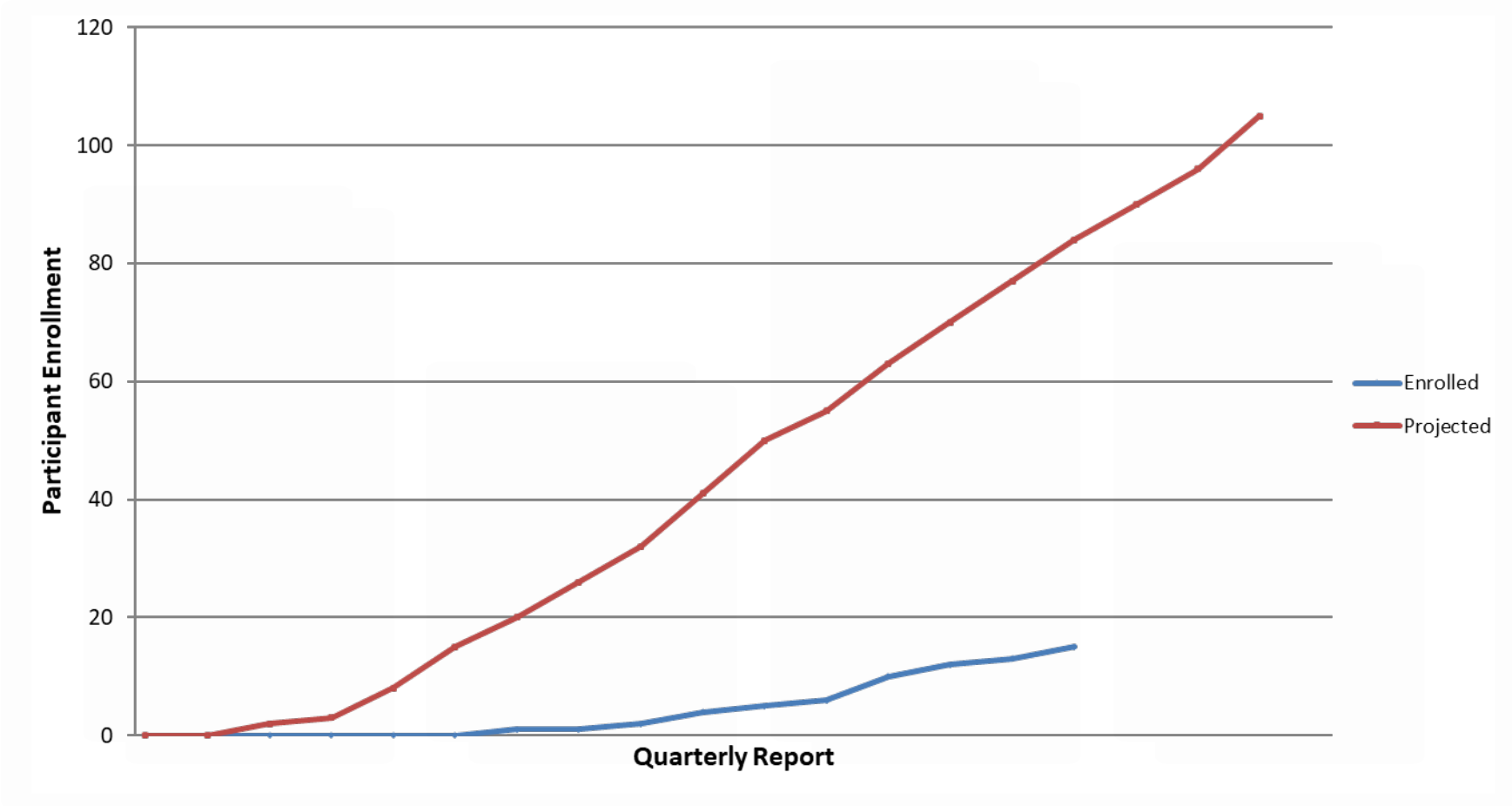


Percent of participants that have completed the study	**3%**

CONSORT Diagram – UT Dallas, Dallas, TX

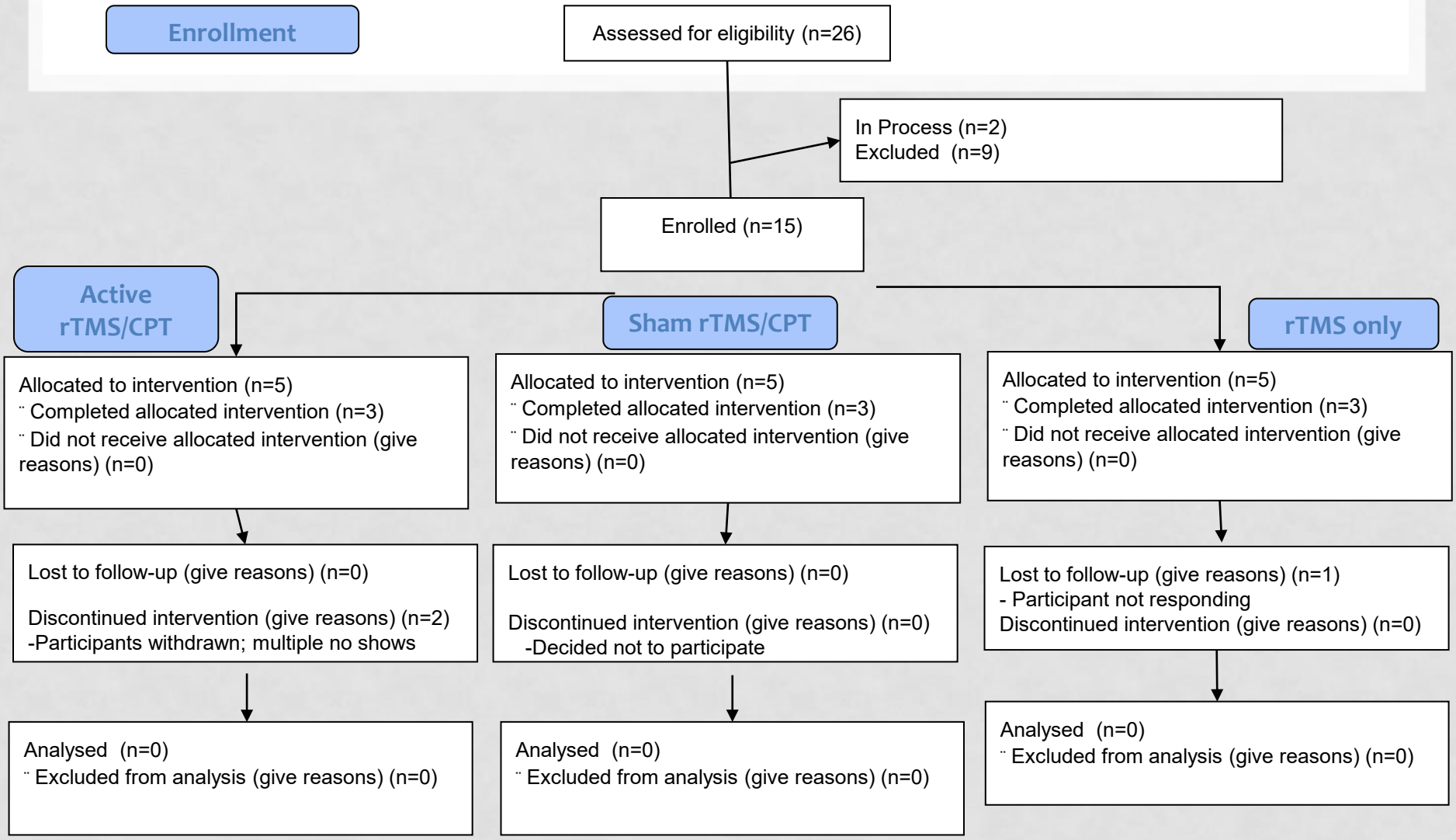


Recruitment and Retention – Metrocare Services, Dallas, TX

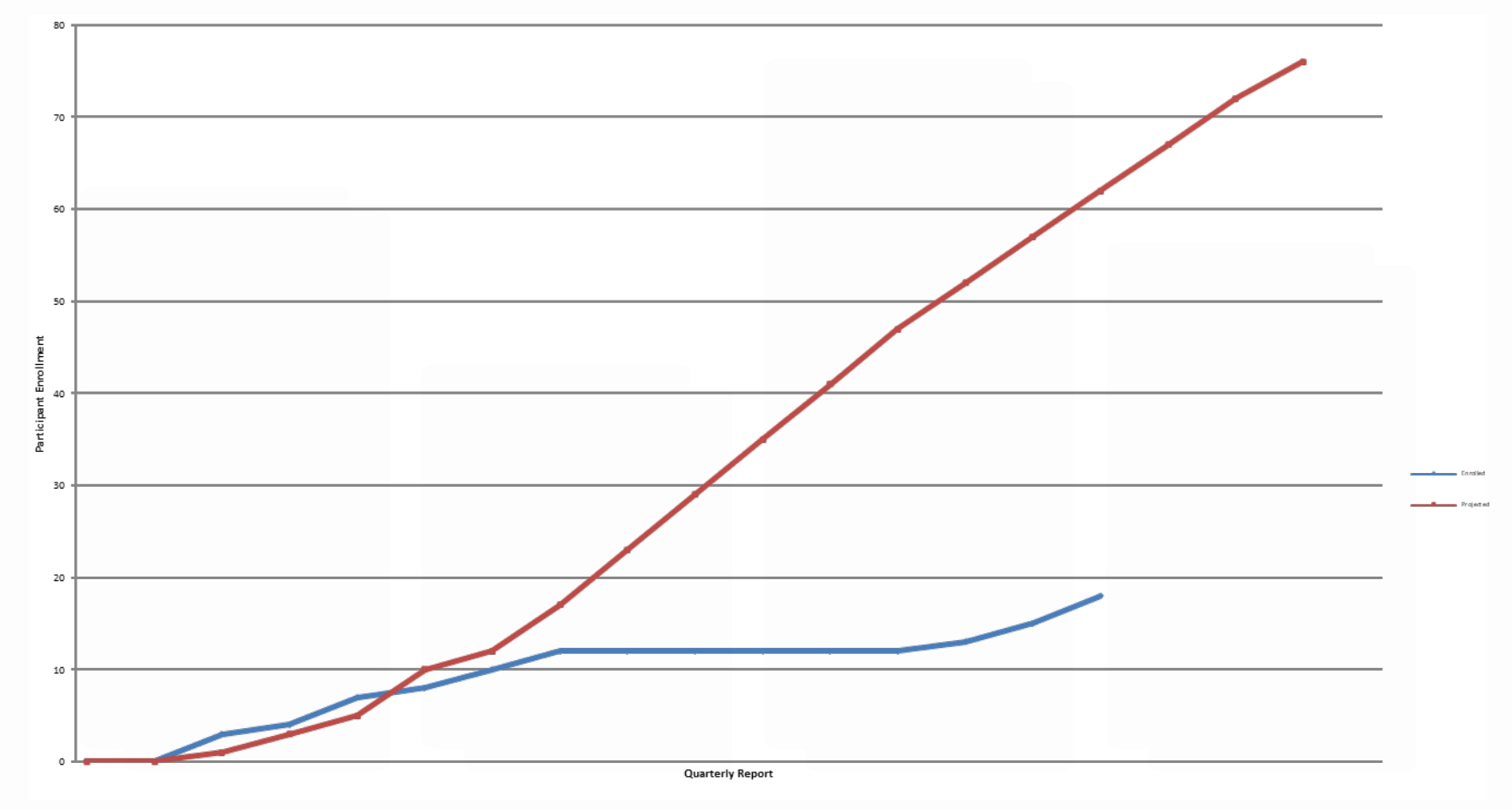


Percent of participants that have completed the study	**2%**

CONSORT Diagram – Metrocare Services, Dallas, TX



Recruitment and Retention – James A. Haley VA Hospital, Tampa, FL & Florida State University, Tallahassee, FL



Percent of participants that have completed the study ***Haley VA site was closed to recruiting in October 2020 and 5 participants reconsented at UTDallas to complete follow up. FSU enrolled participants starting in Y4Q2.***	**7%**

CONSORT Diagram – Haley VA Hospital & Florida State University, FL