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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

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5e. TASK NUMBER

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The University of Texas at Dallas
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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 131 subjects for the study and enrolled 37 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?

PreStudy Tasks – 100% complete

Screening and Treatment Tasks for Aims 1 & 2

Aim 1: *All tasks in progress, except tasks 5-6*

- Task 1: Contact, recruit and screen patients for study enrollment
  - Y1Q1-Y3Q4: 25% complete (goal 369)
- Task 2: Perform pre-treatment neuropsychiatric assessments on participants
  - Yr1Q1-Yr3Q4: 15% complete (goal 242)
- Task 3: Perform active rTMS/CPT, sham rTMS/CPT, or rTMS alone on participants
  - Y1Q1-Y3Q4: 13% complete (goal 242)
- Task 4: Perform post-treatment neuropsychiatric assessments at 1 month, 6 months, and 12 months after last treatment on participant
  - Y1Q1-Y3Q4: 9% complete (goal 141)
- Task 5: Perform longitudinal analyses of neuropsychiatric measures of treatment efficacy
- Task 6: Prepare and submit manuscript on treatment efficacy

Aim 2: *All tasks in progress, except tasks 5-8*

- Task 1: Perform pre-treatment ERPS for threatening stimuli for participants
  - Y1Q1-Y3Q4: 13% complete (goal 242)
- Task 2: Perform pre-treatment fMRIs for threatening stimuli for participants
  - Y1Q1-Y3Q4: 9% complete (goal 187)
- Task 3: Perform post-treatment ERP for threatening stimuli at 6 and 12 months
  - Y1Q1-Y3Q4: 4% complete (goal 141)
- Task 4: Perform post-treatment fMRI for threatening stimuli at 6 and 12 months
  - Y1Q1-Y3Q4: 5% complete (goal 108)
- Task 5 & 6: Perform longitudinal analyses of ERP and fMRI measures of treatment efficacy
- Task 7 & 8: Prepare and submit manuscripts on ERP and fMRI measures of treatment response

What was accomplished under these goals?

We have established the research team and laboratory settings, maintained continued approval of all regulatory documents for all performance locations for the study, and established recruiting procedures. This includes moving the Florida site from Tampa to Tallahassee, and receiving approval for UT Southwestern to be the IRB of Record for all sites. The study is live on ClinicalTrials.gov and we have maintained a Certificate of Confidentiality from NIH. The Fidelity Monitor has reviewed CPT sessions and the Data Safety Monitoring Board is scheduled to meet in August.

We continue to grow our recruiting network and social media presence. We have promoted our project on podcasts, the newspaper, and websites.

We have recruited 131 subjects out of 505 expected and screened 94 subjects. We have enrolled 37 out of 330 expected. Of the 32 randomized, 14 are in active treatment phase, 6 are in follow-up, 6 have completed follow up, and 6 withdrew during treatment or follow up.

The COVID-19 pandemic has had a tremendous impact on recruitment for this study. In March 2020, all three sites were required to stop enrollment and in-person treatment due to the COVID-19 pandemic. UTD resumed enrollment to a limited degree in mid-August 2020, and Metrocare resumed in November 2020 in accordance with institutional policies at each site. Minor changes in protocol to safely administer screening and testing protocols were approved by IRB last year. This includes migrating to an on-line format option for consent, lab tours, assessments and aspects of therapy, reconfiguring space for social distancing, wearing masks, gloves and goggles, providing access to hand washing or hand sanitizing stations, reducing touch points, and adding additional cleaning procedures.

Additionally, during this year, the Tampa James Haley VA site moved to Florida State University. While this process was initiated during COVID-19 restrictions, it has negatively impacted recruitment since the easing of COVID-19 restrictions.

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
- 10 October 2020 – DoD HRPO acceptance of continuing review for all sites
- 27 October 2020 – notified DoD HRPO of study closure at James A. Haley VA Medical Center, University of South Florida IRB
- 16 April 2021 – UT Southwestern IRB approval to add Florida State University to the protocol; UT Southwestern is now the IRB of Record for all sites, including UT Southwestern, UT Dallas, Metrocare Services and Florida State University
- 26 April 2021 – notified DoD HRPO of addition of Florida State University as a site
- 16 June 2021 – UT Southwestern acceptance of continuing review for all sites
- 23 July 2021 – DoD HRPO acceptance of continuing review for all sites, including addition of FSU

Number of subjects recruited/original planned target: 131/505
Number of subjects screened/original planned target: 94/505
Number of patients enrolled/original planned target: 37/330

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?

This next year, we will continue to focus on Aim 1, Task 1-4 and Aim 2, Task 1-4 as described in the SOW. Recruiting efforts are a priority, and we will continue to actively pursue partnerships for other avenues of recruitment. FSU began recruiting in this 4th quarter and plan to enroll their first participant in the next quarter. All sites will mitigate risks of Covid-19, by following protocols, including using an on-line format where possible, practicing social distancing, and increasing safety protocols.

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

Covid-19 pandemic continues to greatly impact recruitment, and we are realistic about the lasting effects of the pandemic. We are monitoring the number of Covid-19 cases in our area, following local and CDC guidelines, and conducting screening and testing protocols on-line where possible. Other safety measures include reconfiguring space for social distancing, wearing masks, gloves and goggles, providing access to hand washing or hand sanitizing stations, reducing touch points, and adding additional cleaning procedures.

While there has been resumption of recruiting activities, there has been other issues related to Covid-19 that reduce ease of enrollment including lack of scheduled meetings/events to recruit from, continued reticence from subjects to participate in "in-person" studies, and persistent elevated infection rates in the regions that sites are located. Given the PTSD patients' symptoms including avoidance, this symptom which already provides a reluctance of these patients to seek treatment was exacerbated by the Covid-19 shutdowns and restrictions

We are constantly working to improve recruitment and reach our overall recruitment goals, and we are putting extra effort into recruitment efforts to adjust for delays.

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.

- **Other Products**

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

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

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

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

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

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

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

Name: Jill Ritter, Research Manager, UT Dallas – No change

Name: Kelsey Watson, Research Assistant, UT Dallas – No change

Name: Justin Jacqmain, Research Assistant, UT Dallas – No change

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

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

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

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

Name: Isabelle Taylor, Research Program Manager, Florida State University – No change

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

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

Name: Christina Riccardi, PhD
Project Role: CPT Therapist, Florida State University
Nearest person month worked: 1 month
Contribution to Project: CPT and CPT training; advising on recruiting

Name: Chelsea Fiduccia, PhD, Co-Investigator
Project Role: Co-Investigator, Clinic Director, Metrocare Services of Dallas
Nearest person month worked: 1 month
Contribution to Project: Oversight of operations at Metrocare Services; Coordination of Cognitive Processing Therapy between all therapists; CPT

Name: Jordan Petry
Project Role: Research Assistant, Metrocare Services of Dallas
Nearest person month worked: 1 month
Contribution to Project: Assists in the administration of/administers rTMS treatment; recruitment and screening procedures; coordination and scheduling of visits, data collection/entry, and reporting.

Name: Tanya Mac
Project Role: Outreach Director, Metrocare Services of Dallas
Nearest person month worked: 1 month
Contribution to Project: Assists in recruitment.

Name: Nicolette Aguon
Project Role: Intake Coordinator, Metrocare Services of Dallas
Nearest person month worked: 1 month
Contribution to Project: Assists in recruitment and connecting interested participants with screening.

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

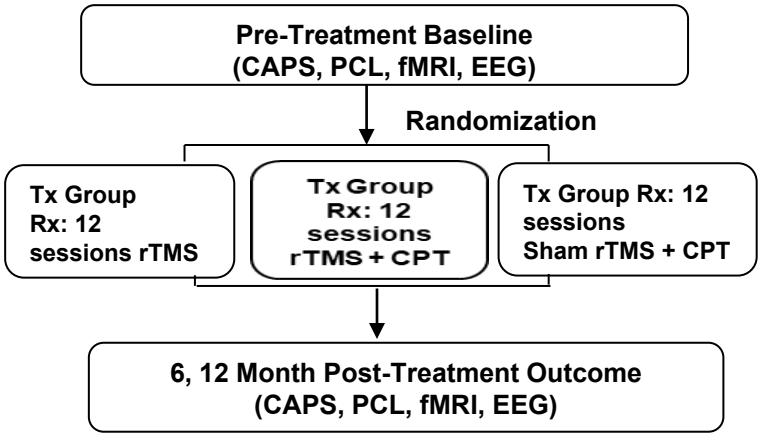
Log # BA160594; Award # W81XWH-18-1-0464

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	2018	2019	2020	2021	2022
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

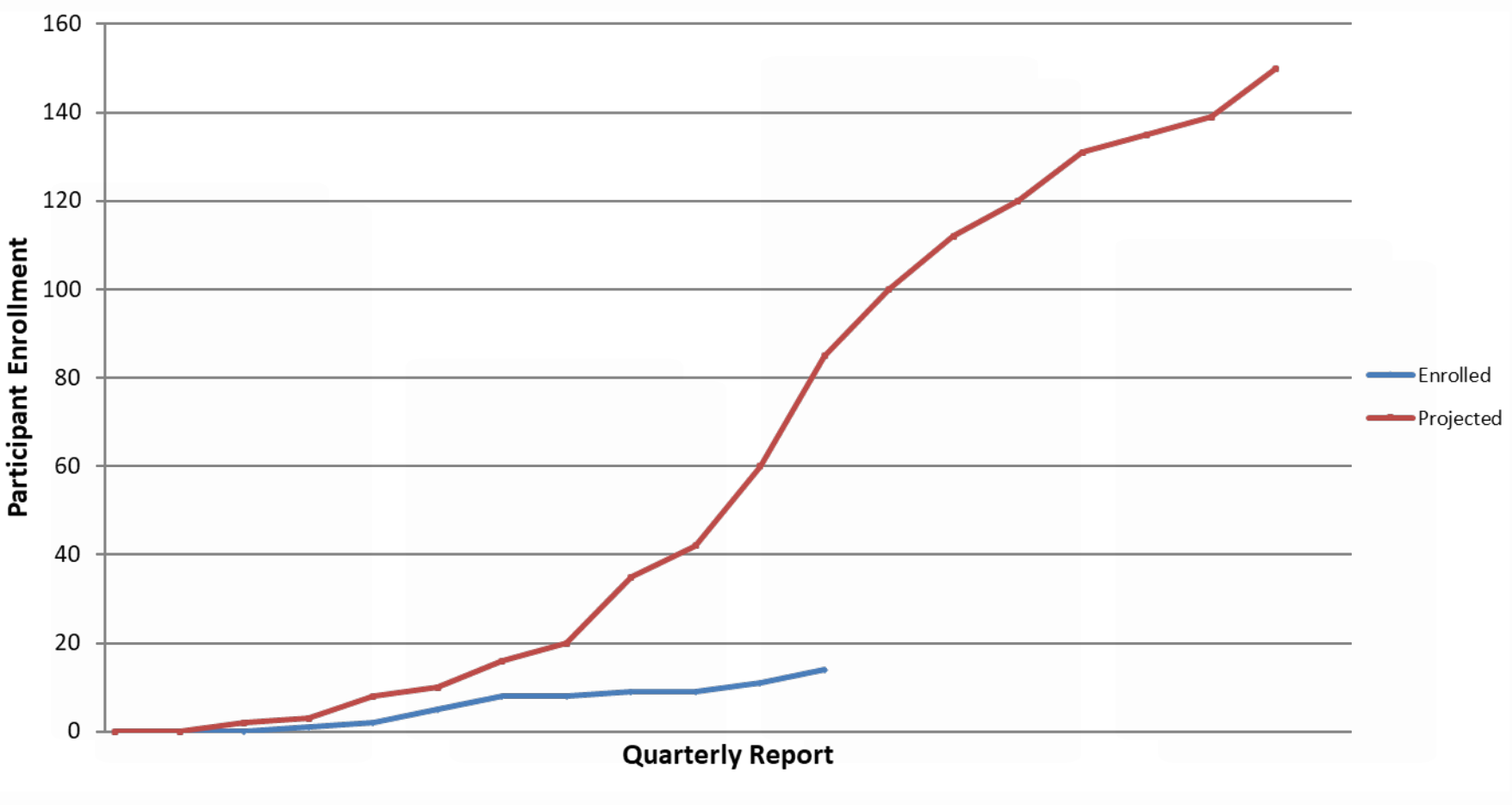
Budget Expenditure to Date

Projected Expenditure: $4,529,275

Actual Expenditure: $2,728,472

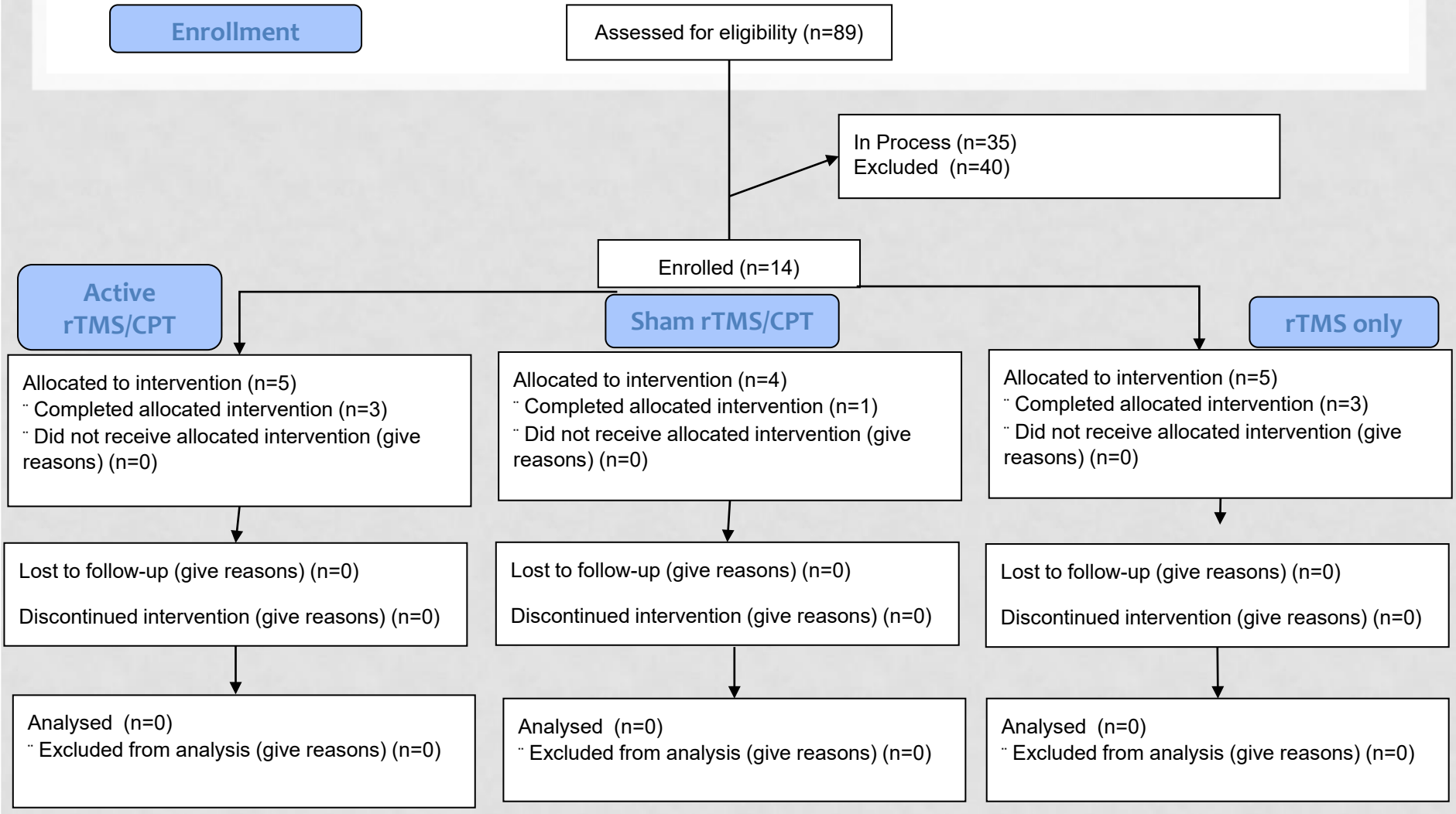
Updated: 1 Aug 2021

Recruitment and Retention – UT Dallas, Dallas, TX

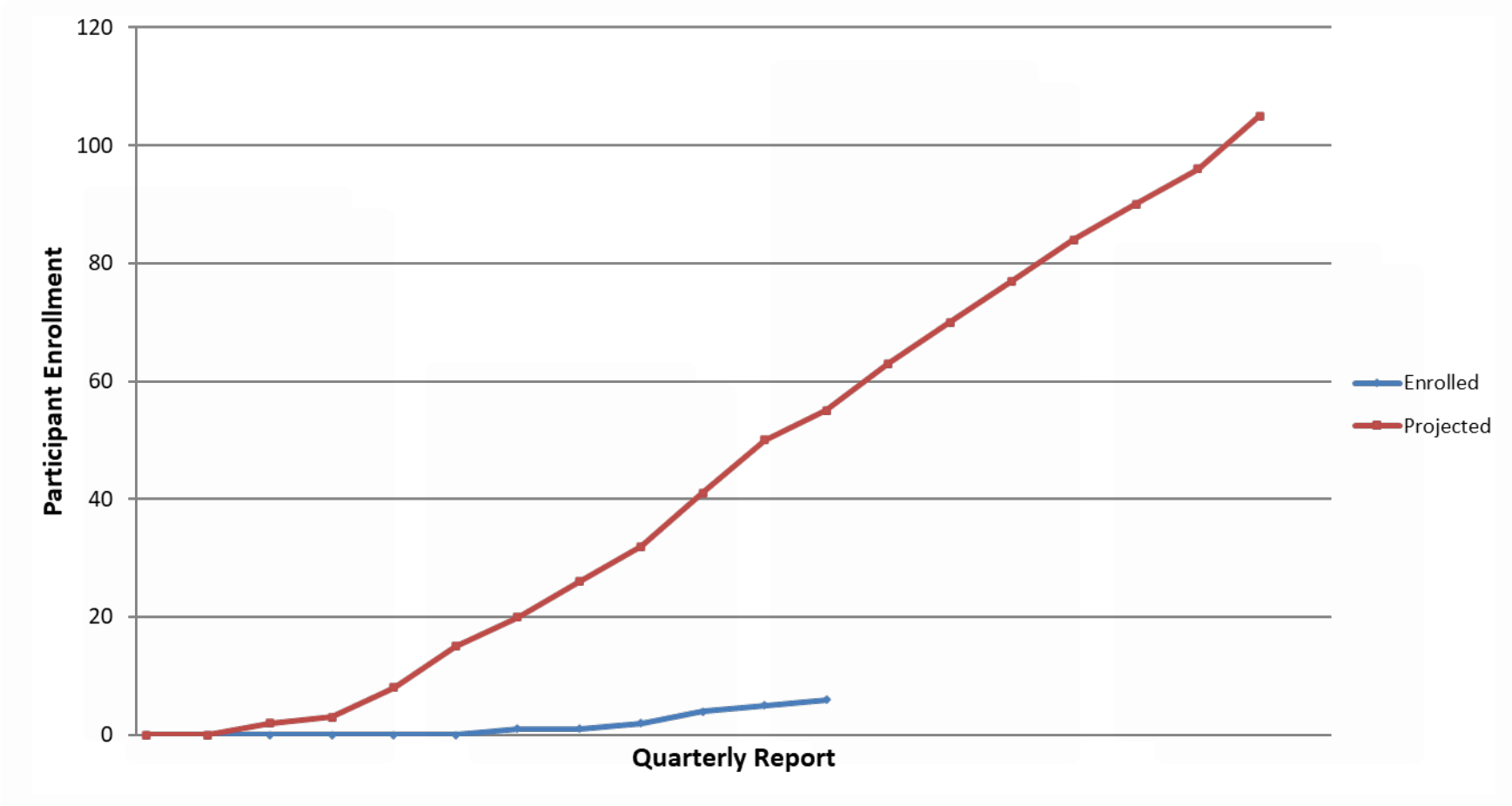


Percent of participants that have completed the study	**1%**

CONSORT Diagram – UT Dallas, Dallas, TX

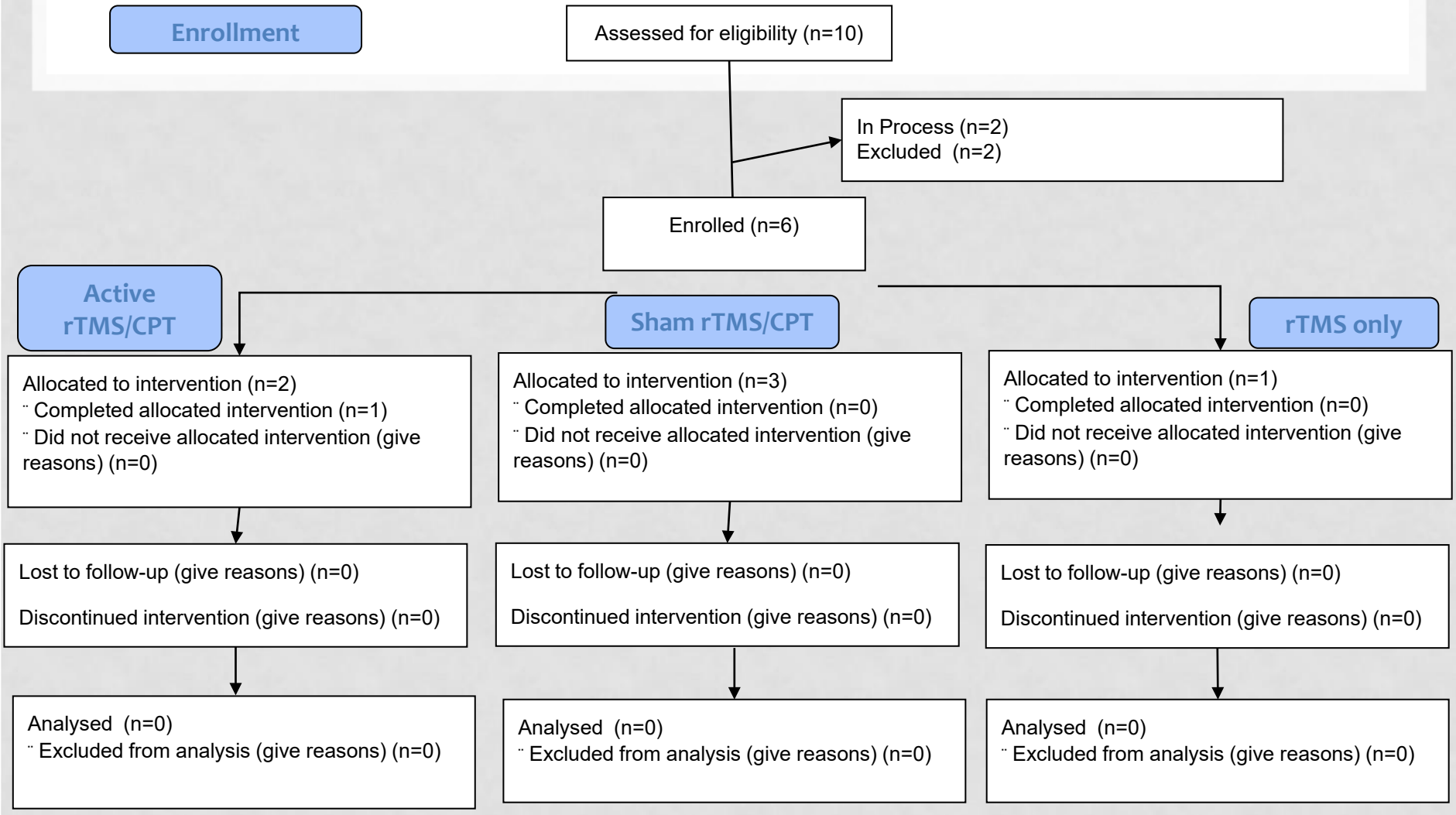


Recruitment and Retention – Metrocare Services, Dallas, TX

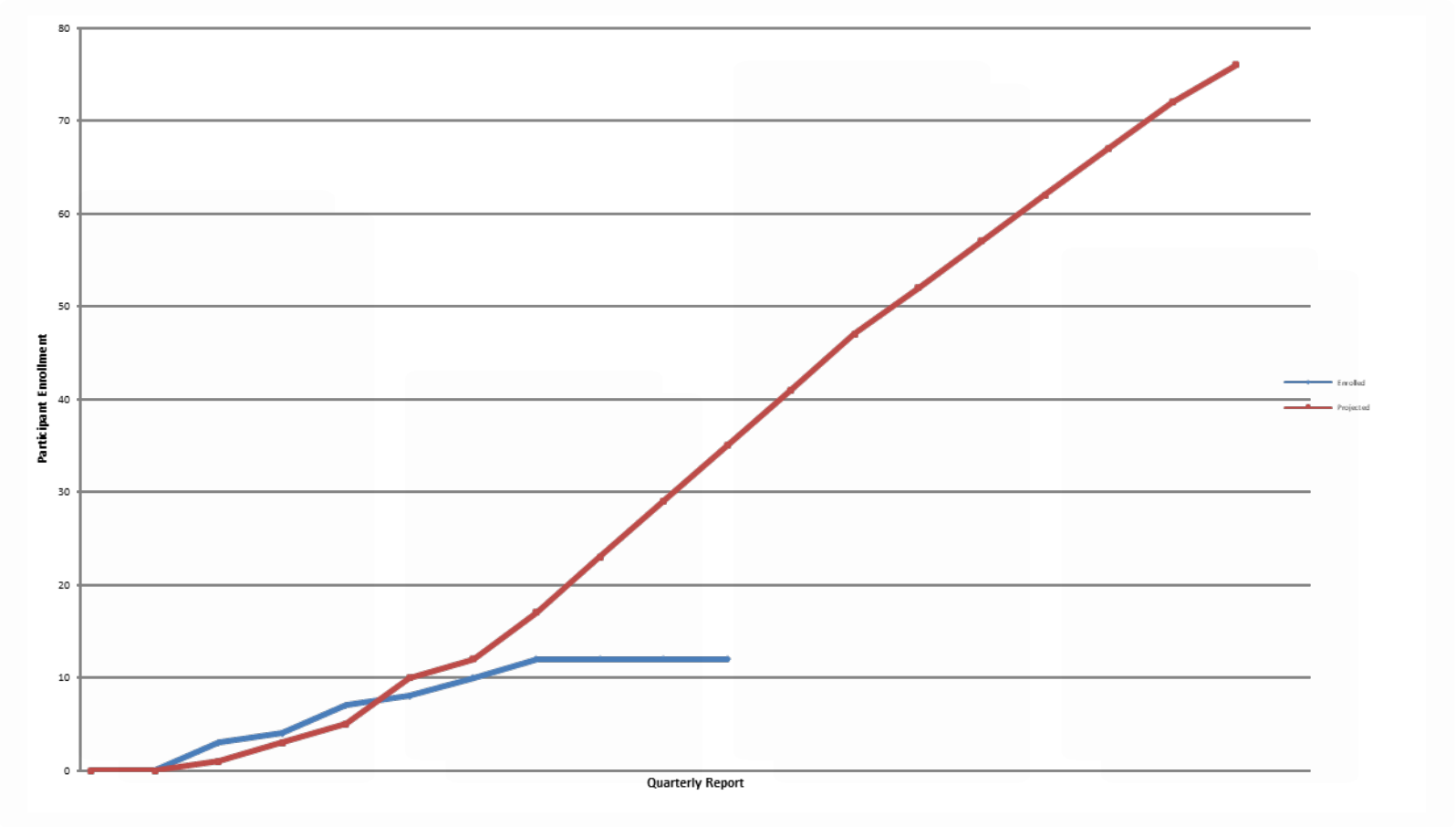


Percent of participants that have completed the study	**0%**

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 projected to start enrolling next quarter.***	**5%**

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