AWARD NUMBER: W81XWH-18-1-0464

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 75080

REPORT DATE: August 2019

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
August 2019	Annual	1 Aug 2018 - 31 Jul 2019

4. TITLE AND SUBTITLE
Multi-site confirmatory efficacy treatment trial of PTSD

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-18-1-0464

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
John Hart Jr., MD

E-Mail: jhart@utdallas.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The University of Texas at Dallas
800 West Campbell Road,
Richardson, TX 75080

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

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, obtained approval of all regulatory documents for all performance locations for the study, and established recruiting procedures. We have screened 63 subjects for the study and enrolled 8 subjects in the baseline testing and treatment phase of the study.

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified		19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Table of Contents

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?

1. Obtain approval from IRB – 100% complete
    a. Obtain UTD and UTSW IRB approvals
    b. Obtain Metrocare IRB approval
    c. Obtain USF IRB approval
2. Obtain lab space; purchase, set-up, and testing for rTMS and EEG equipment at each site – 85% complete
3. Recruit personnel – 100% complete
4. Training staff – 85% complete
    a. UTD staff prepares materials for training other sites – 100% complete
    b. Appropriate staff trained in EEG, rTMS, and CPT – 85% complete
        i. Staff at Metrocare trained in rTMS administration
        ii. Training of existing or new staff in EEG at Haley VA
5. Recruiting procedures – 100% complete
    a. Establish recruiting procedures
    b. Training of staff on recruiting procedures
6. Prepare and submit regulatory documents to HRPO – 100% complete
7. Contracting/recruiting of patients for study enrollment – 12% complete
8. Screening of patients for study enrollment – 8% complete
9. Preform pre-treatment neuropsychological assessments, EEG, and fMRI – 2% complete
10. Perform active rTMS/CPT, sham rTMS/CPT, or rTMS alone on 330 patients – 0.3% complete
11. Perform follow-up neuropsychiatric assessments and EEG at 1 month – 0% complete
12. Perform follow-up neuropsychiatric assessments, EEG, and fMRI at 6 and 12 months – 0% complete
    a. Prepare and perform preliminary analysis in last 6 months of project.
13. Perform longitudinal analysis of neuropsychiatric, EEG, and fMRI measures of treatment efficacy – 0% complete

What was accomplished under these goals?

We have established the research team (including hiring Project Coordinators and Research Assistants), laboratory setting (including ordering equipment and setting up EEG systems at UT Dallas and the Tampa VA), obtained approval of all regulatory documents for all performance locations for the study, and established recruiting procedures. The study is live on ClinicalTrials.gov and we have obtained a Certificate of Confidentiality from NIH.

Our staff has attended numerous recruiting events, and we have established a large recruiting network and social media presence. We have promoted our project on podcasts, the newspaper, and websites.

We have recruited 63 subjects out of 505 expected. We have screened 43 subjects out of 505 expected. We have enrolled 8 out of 330 expected. All 8 subjects have completed baseline testing (neuropsychiatric assessments, EEG, and fMRI (Dallas only)). Two subjects withdrew (please see attached consort diagrams). Currently, 1 subject awaits randomization, 4 subjects are in the treatment phase, and 1 has completed treatment and has been scheduled for a one-month follow-up.

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?

We will continue seeking new avenues of publicity for our project in order to boost recruitment. Our independent Fidelity Monitor, Dr. Ryan Holliday, will begin reviewing therapy sessions shortly to make sure the Cognitive Processing Therapy is proceeding correctly and uniformly. In a few weeks, the project PI, Dr. Hart, will present to the MOMRP PTSD Treatment IPR on the project's progress. We will also continue to analyze data and publish results from the preliminary study on which this study is based.

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

We experienced some delay in obtaining human subject approvals for all sites, but during that time we were building recruiting networks and creating recruiting materials so that when approvals were obtained we were able to immediately disseminate information.

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

There has been some delay in spending, particularly on staffing and participant payments, because recruiting for the project only got underway a few months ago after obtaining human subjects approvals for all sites.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

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.

DeLaRosa, B., Spence, J., Didehbani, N., Tillman, G., Motes, M., Bass, C., Kraut, M., Hart Jr., J. (under review). Neurophysiology of threat processing bias in combat-related post-traumatic stress disorder. Human Brain Mapping.

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?

Name: John Hart, Jr., MD
Project Role: Principal Investigator
Nearest person month worked: 1
Contribution to Project: Oversight of entire project, study design, methods, recruiting procedures, fMRI protocols, rTMS training, and development of data safety monitoring board

Name: F. Andrew Kozel, MD
Project Role: Co-Investigator, Site PI at James A. Haley VA Hospital
Nearest person month worked: 1
Contribution to Project: Coordination of protocol and testing assessments, study design, and methods

Name: Elizabeth "Ellen" Morris, PhD
Project Role: Project Coordinator/CPT Therapist
Nearest person month worked: 6
Contribution to Project: setting up recruiting network, CPT training, and protocol development

Name: Christina "Tina" Bass, M.S., LPC
Project Role: CPT Therapist
Nearest person month worked: 4
Contribution to Project: CPT training and protocol development

Name: Sarah Sprinkle
Project Role: Research Manager
Nearest person month worked: 4
Contribution to Project: Coordination of protocol and testing assessments between performance sites, submission and revisions of regulatory paperwork, and development of recruiting tools

Name: Mary Turner, PhD
Project Role: Independent Evaluator
Nearest person month worked: 4
Contribution to Project: Protocol development, testing assessments

Name: Barbara McKenzie
Project Role: Project Coordinator
Nearest person month worked: 12
Contribution to Project: Coordination of protocol and testing assessments between performance sites, submission and revisions of regulatory paperwork, and development of protocol

Name: Michael Motes, PhD
Project Role: Co-Investigator
Nearest person month worked: 1
Contribution to Project: Protocol development, study design, authored EEG manual, testing and set-up of EEG equipment, development of fMRI protocol and analysis methods

Name: Michael Kraut, MD, PhD
Project Role: Co-Investigator
Nearest person month worked: 1
Contribution to Project: Protocol development, study design, development of fMRI protocol and analysis methods

Name: John Burruss, MD
Project Role: Co-Investigator, Site PI at Metrocare Services of Dallas
Nearest person month worked: 1
Contribution to Project: Coordination of protocol and testing assessments between performance sites, identification of appropriate personnel at Metrocare performance site, and recruiting

Name: Kelsey Watson
Project Role: Research Assistant, UT Dallas
Nearest person month worked: 6
Contribution to Project: Development of recruiting tools, identification of recruiting relationship, gathering of study materials and supplies, editing of study materials, assisting Dr. Morris.

Name: Demian Obregon
Project Role: Physician
Nearest person month worked: 1
Contribution to Project: Assisting with recruiting and rating of neuropsychological tests.

Name: Katherine Ralston, MA, MS
Project Role: Research Assistant
Nearest person month worked: 6
Contribution to Project: recruiting, screening, coordination and scheduling of visits, data entry, reporting, and EEG.

Name: Amy Williams, PhD
Project Role: Co-Investigator
Nearest person month worked: 2
Contribution to Project: coordination of Cognitive Processing Therapy between all therapists, set up of project at Metrocare Services, and CPT training.

Name: Kimberly Van Trees
Project Role: Research Assistant
Nearest person month worked: 1
Contribution to Project: sets up rTMS coil for administration, is only unblended person in the study to add with group assignments and in the blinding of all other study personnel.

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. 1 for each site.

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

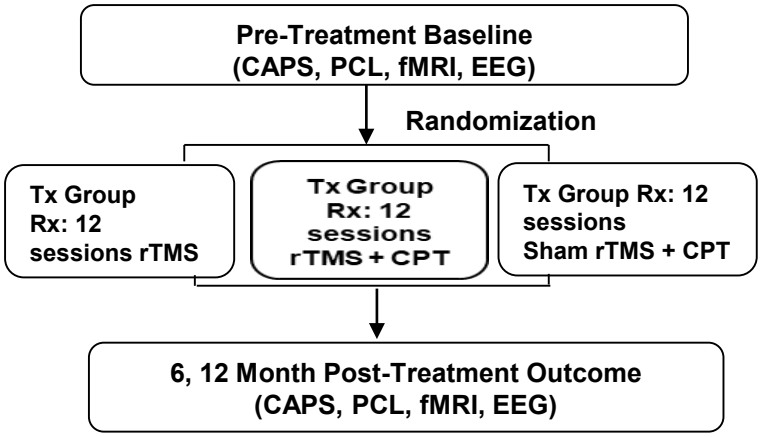
Log # BA160594; Award # W81XWH-18-1-0464

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) Haley Veterans' Hospital in Tampa, 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 Goal

☐ Approval of regulatory documents

CY18 Goals

☐ Recruiting 30 subjects in treatment across sites

CY18-21 Goal

☐ Enrolling 330 subjects in the study

CY22 Goal

☐ Analyzing data

Comments/Challenges/Issues/Concerns

- N/A

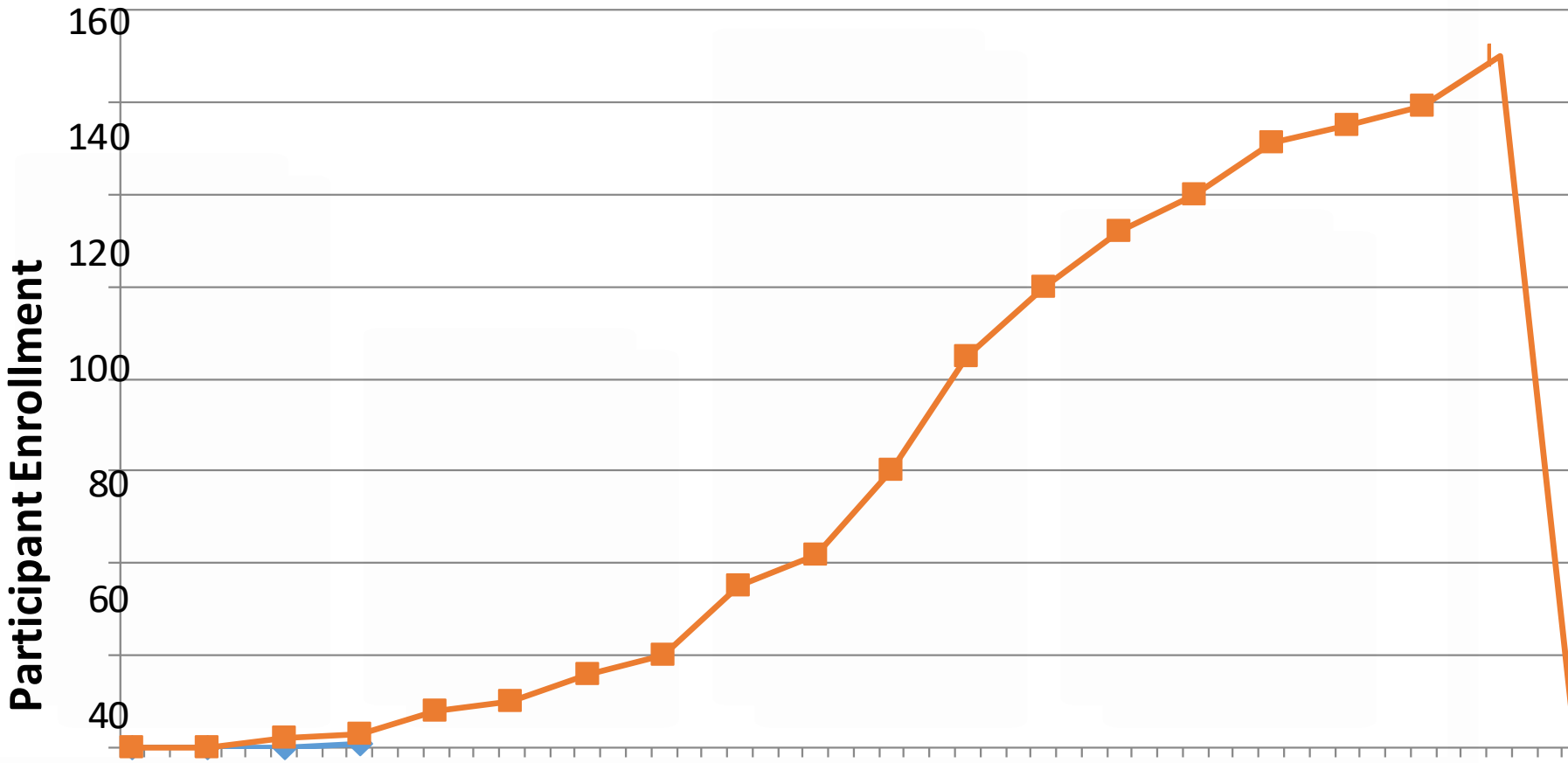
Budget Expenditure to Date

Projected Expenditure: $1,561,671

Actual Expenditure: $663,194

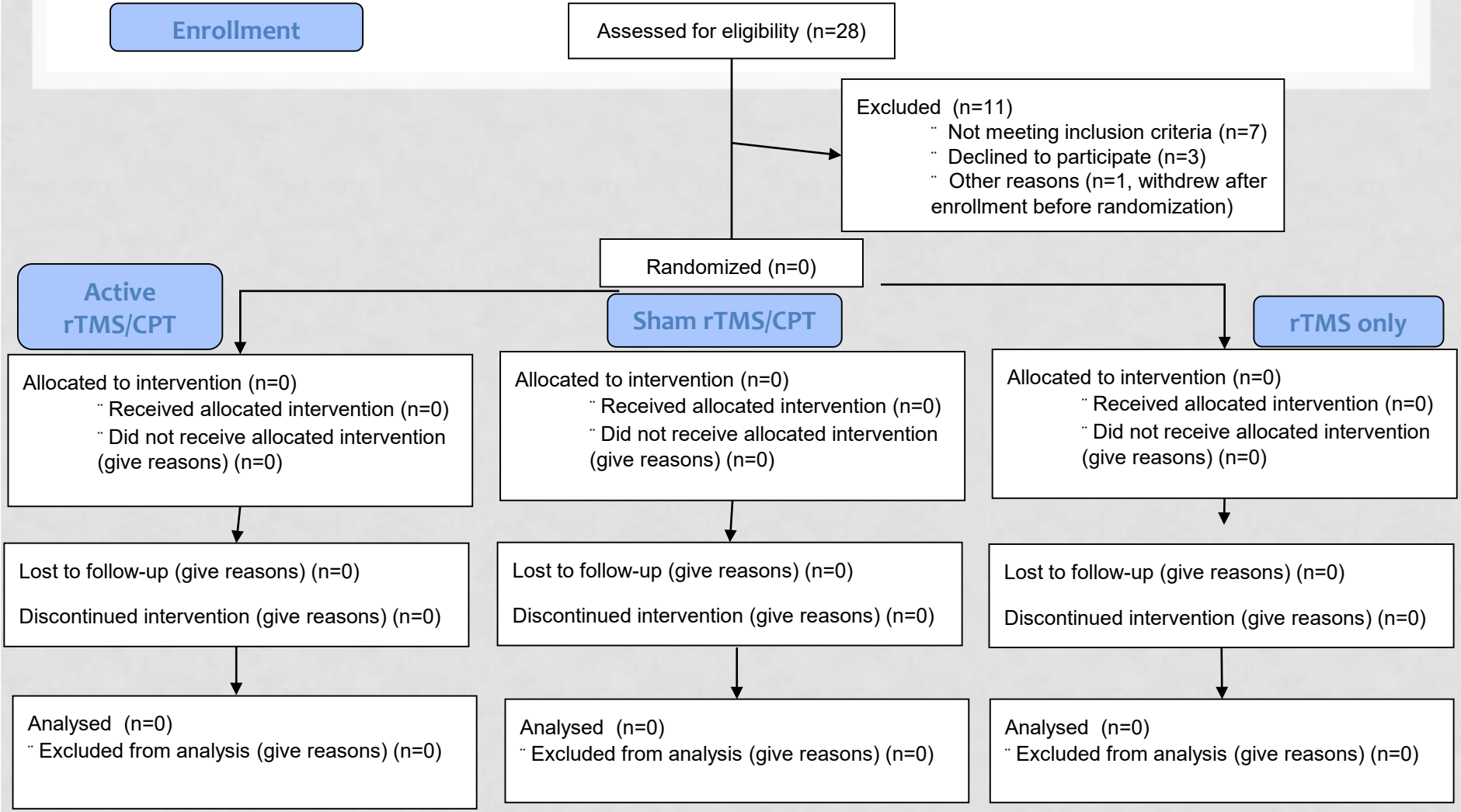
Updated: 30 August 2019

Recruitment and Retention – UT Dallas, Dallas, TX

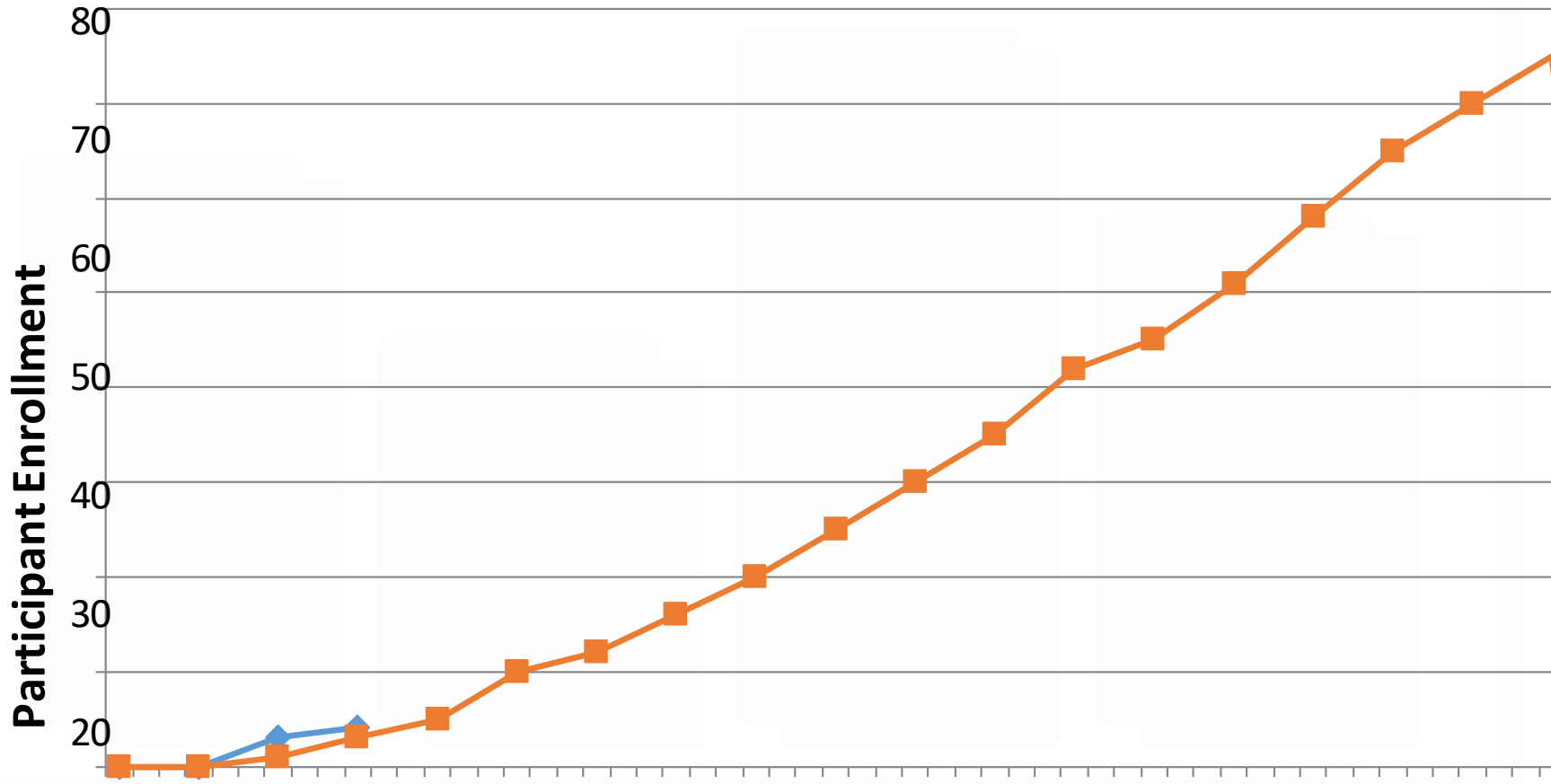


Percent of participants that have completed the study	**0%**

CONSORT Diagram – UT Dallas, Dallas, TX

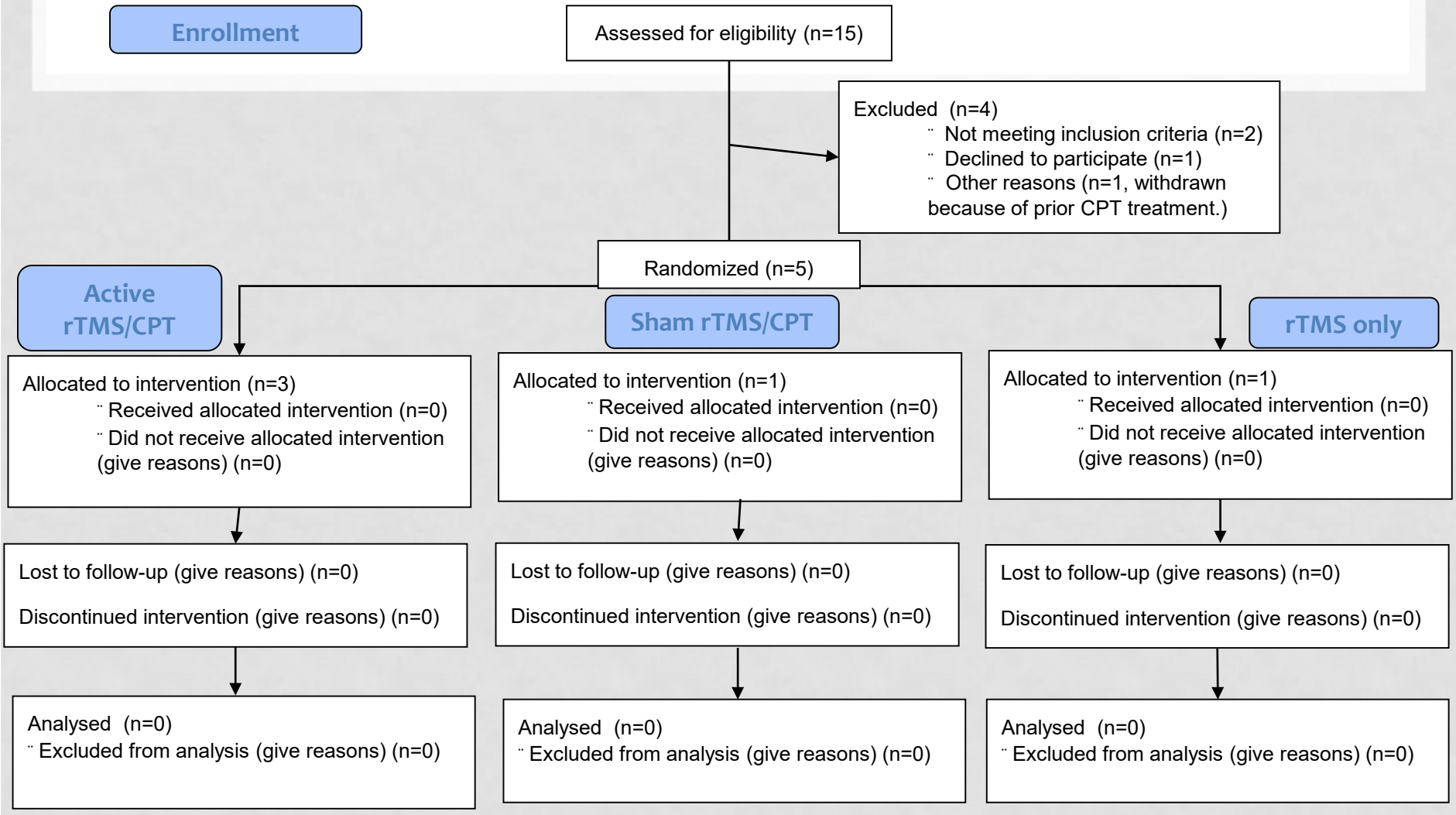


Recruitment and Retention – James A. Haley VA Hospital, Tampa, FL

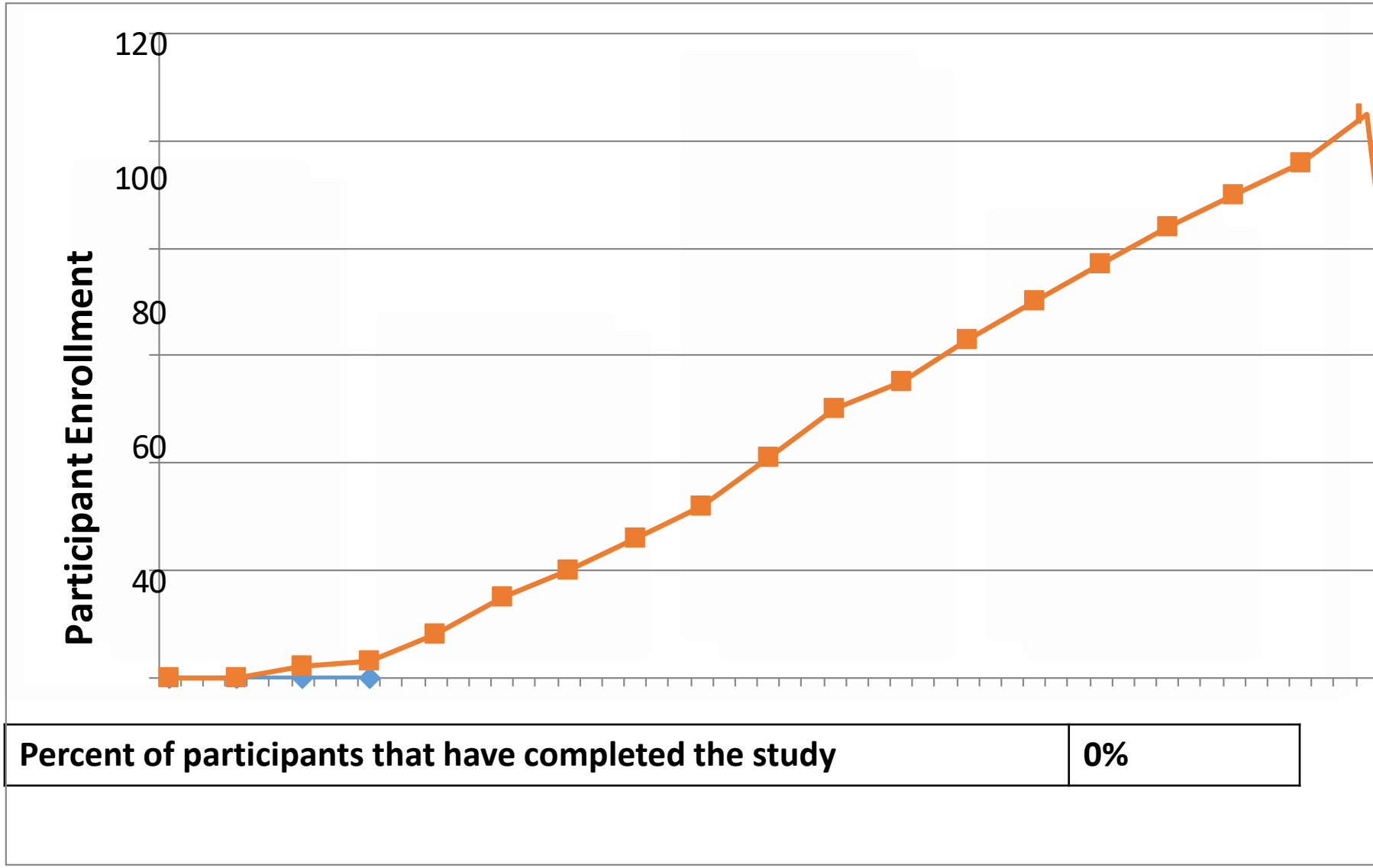


Percent of participants that have completed the study	**0%**

CONSORT Diagram – James A. Haley VA Hospital, Tampa, FL



Recruitment and Retention – Metrocare Services, Dallas, TX



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

CONSORT Diagram – Metrocare Services, Dallas, TX