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

REPORT DATE: August 2020

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 2020	Annual	8/1/2019 – 7/31/2020

4. TITLE AND SUBTITLE

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

5a. CONTRACT NUMBER
W81XWH-18-1-0464

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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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, maintained approval of all regulatory documents for all performance locations for the study, and established recruiting procedures. We have recruited 102 subjects for the study and enrolled 27 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)

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

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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?

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 – 100% complete
3. Recruit personnel – 100% complete
4. Training staff – 100% complete
    a. UTD staff prepares materials for training other sites – 100% complete
    b. Appropriate staff trained in EEG, rTMS, and CPT – 100% 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 – 20% complete
8. Screening of patients for study enrollment – 13% complete
9. Preform pre-treatment neuropsychological assessments, EEG, and fMRI – 8% complete
10. Perform active rTMS/CPT, sham rTMS/CPT, or rTMS alone on 330 patients – 8% complete
11. Perform follow-up neuropsychiatric assessments and EEG at 1 month – 3% complete
12. Perform follow-up neuropsychiatric assessments, EEG, and fMRI at 6 and 12 months – 2% 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 and laboratory settings, maintained continued 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. The Fidelity Monitor has reviewed CPT sessions and the Data Safety Monitoring Board has met.

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 102 subjects out of 505 expected and screened 64 subjects. We have enrolled 27 out of 330 expected. Currently, 6 subjects are pending consent/baseline testing and 21 are randomized. Of the 21 randomized, 1 is pending treatment, 5 are in active treatment phase, 12 have completed treatment and are in follow-up post 1 or post 6 months and 3 withdrew.

We had to stop enrollment and treatment as of 20 March 2020 due to the COVID-19 pandemic. After that point, we focused on data entry, data clean-up and other tasks that can be handled remotely. The UTD site has received approval to resume in person treatment beginning 15 August 2020. The other sites are currently seeking approval to resume.

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 increase recruiting efforts and will continue to actively pursue partnerships for other avenues of recruitment. We will mitigate risks of Covid-19, by migrating procedures to 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

In March 2020, all three sites were required to stop enrollment and in-person treatment due to the Covid-19 pandemic, and HRPO was notified of the suspension. In the next quarter, we expect to resume in person treatment in accordance with institutional policies at all sites while ensuring the health and safety of our subjects. While we are realistic about the lasting effects of the pandemic, we are working on minimizing its impact by exploring ways to safely administer screening and testing protocols. 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.

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.

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.L., Spence, J.S., Didehbani, N., Tillman, G.D., Motes, M.A., Bass, C., Kraut, M.A., Hart, J., Jr. (2020). Neurophysiology of threat processing bias in combat-related post-traumatic stress disorder. Human Brain Mapping, 41(1), 218-229. doi: 10.1002/hbm.24800; accepted; federal support acknowledged

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, James A. Haley VA Hospital – 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: Amy Williams, PhD, Co-Investigator, Metrocare Services of Dallas – No change

Name: Kathrine Makovec, Research Assistant, Metrocare Services – 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: Rachel O'Hair, 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 – No change

Name: Barbara McKenzie, Project Coordinator, James A. Haley VA Hospital, FL – No change

Name: Kimberly Van Trees, RN, Research Assistant, James A. Haley VAH, FL – No change

Name: Christine Burke, RN, Certified TMS Administrator, James A. Haley VAH, FL – No change

Name: Laura Bajor, DO, Certified CPT Therapist, James A. Haley VAH, FL – No change

Name: Shannon Miles, PhD, Certified CPT Therapist, James A. Haley VAH, FL – No change

Name: Sandra Mutolo, MSW, Trained CAPS/SCID Rater, James A. Haley VAH, FL – No change

Name: Gregory Sullivan, MD, rTMS Physician, James A. Haley VAH, FL – 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

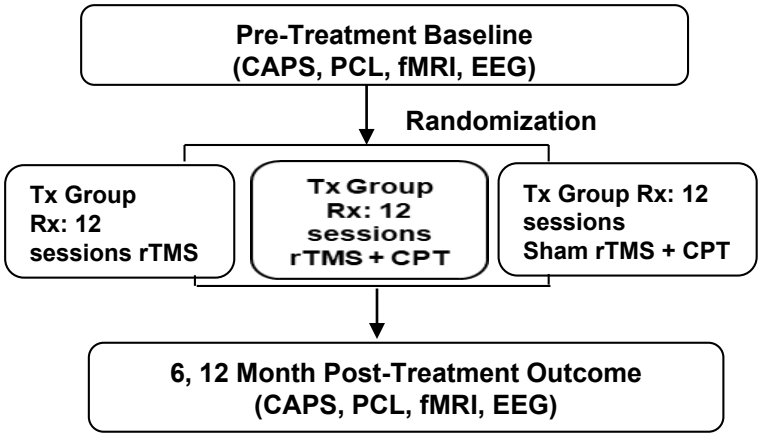
Log # BA160594; Award # W81XWH-18-1-0464

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) 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

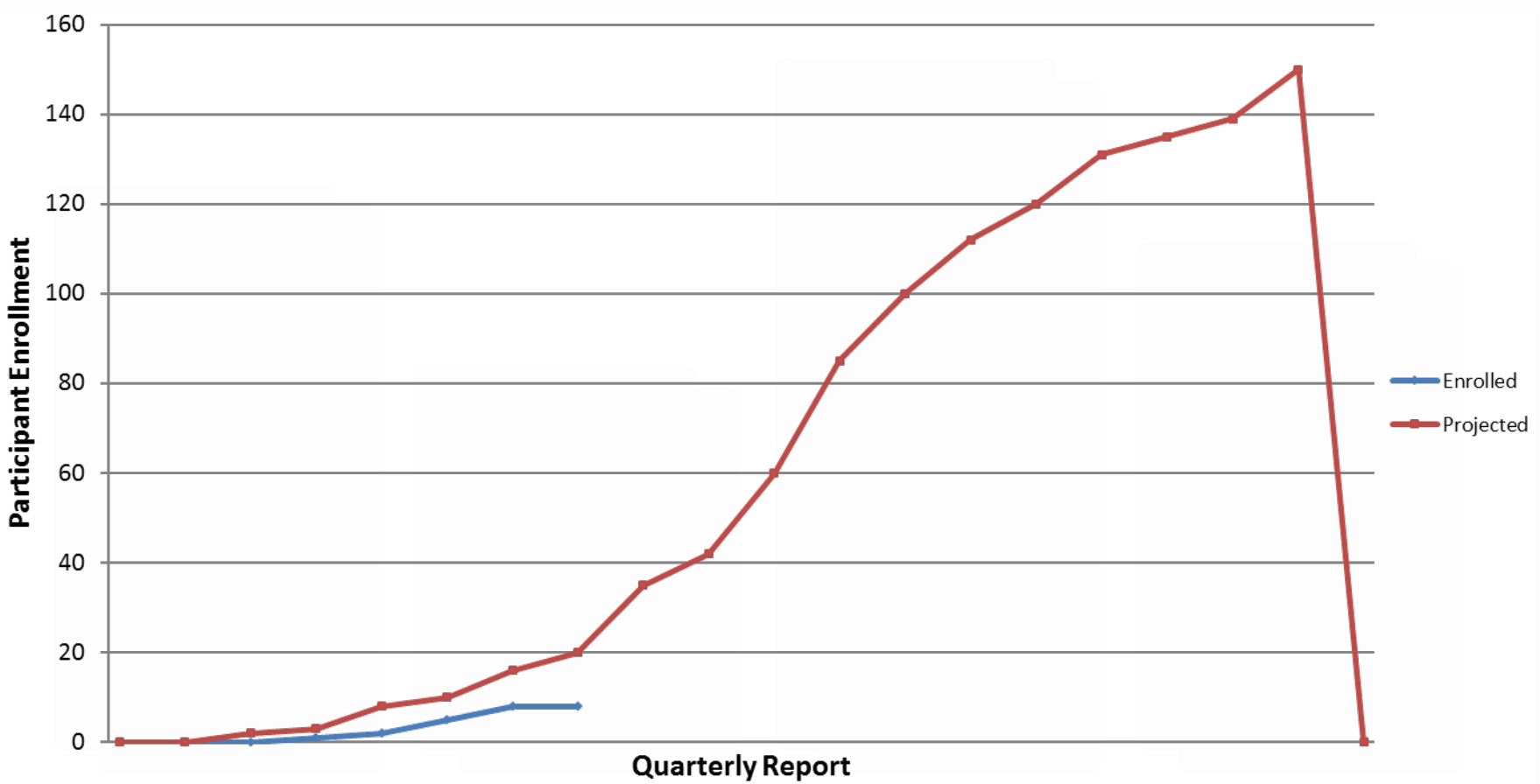
Budget Expenditure to Date

Projected Expenditure: $3,025,165

Actual Expenditure: $1,728,713

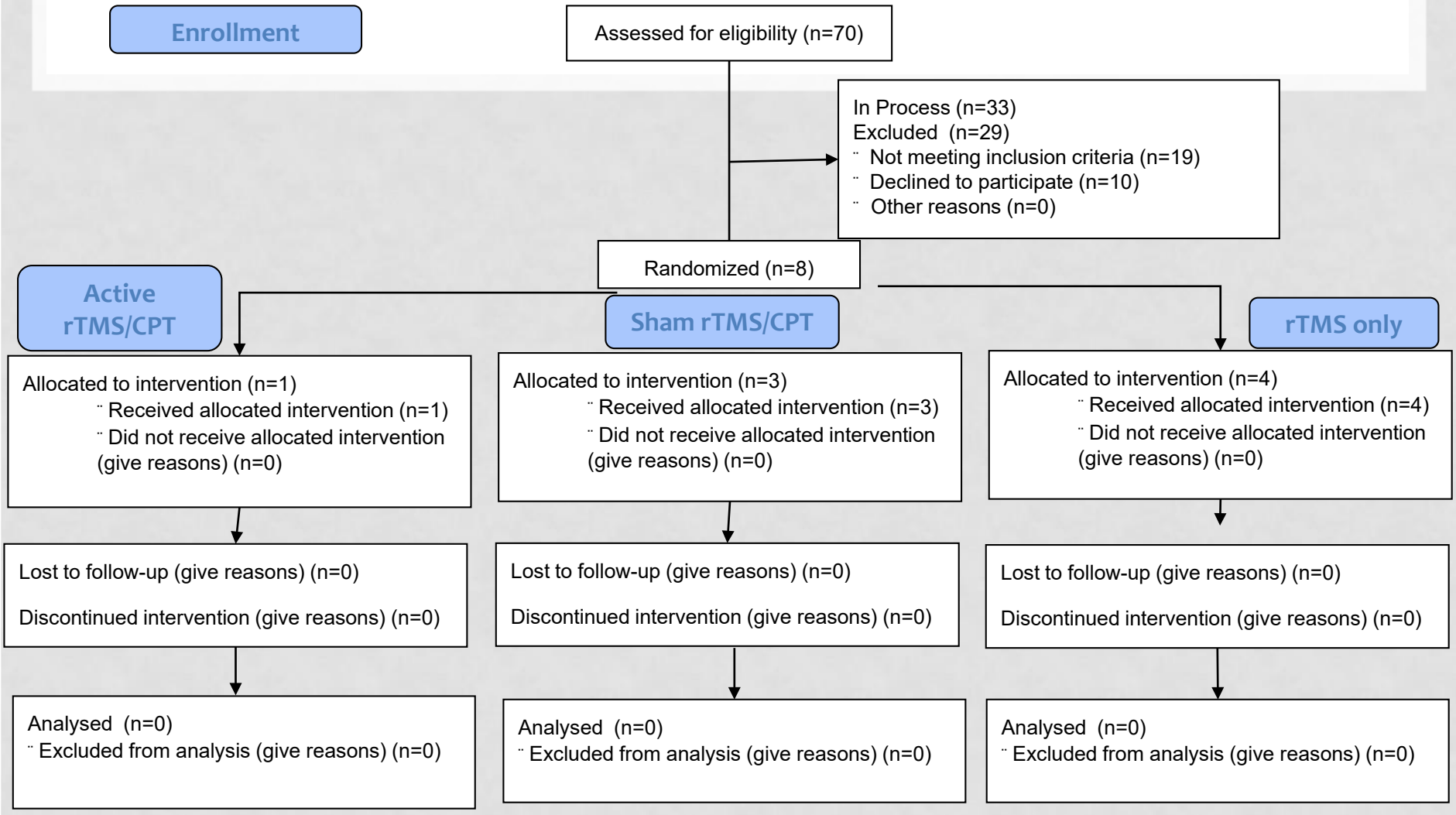
Updated: 31 July 2020

Recruitment and Retention – UT Dallas, Dallas, TX

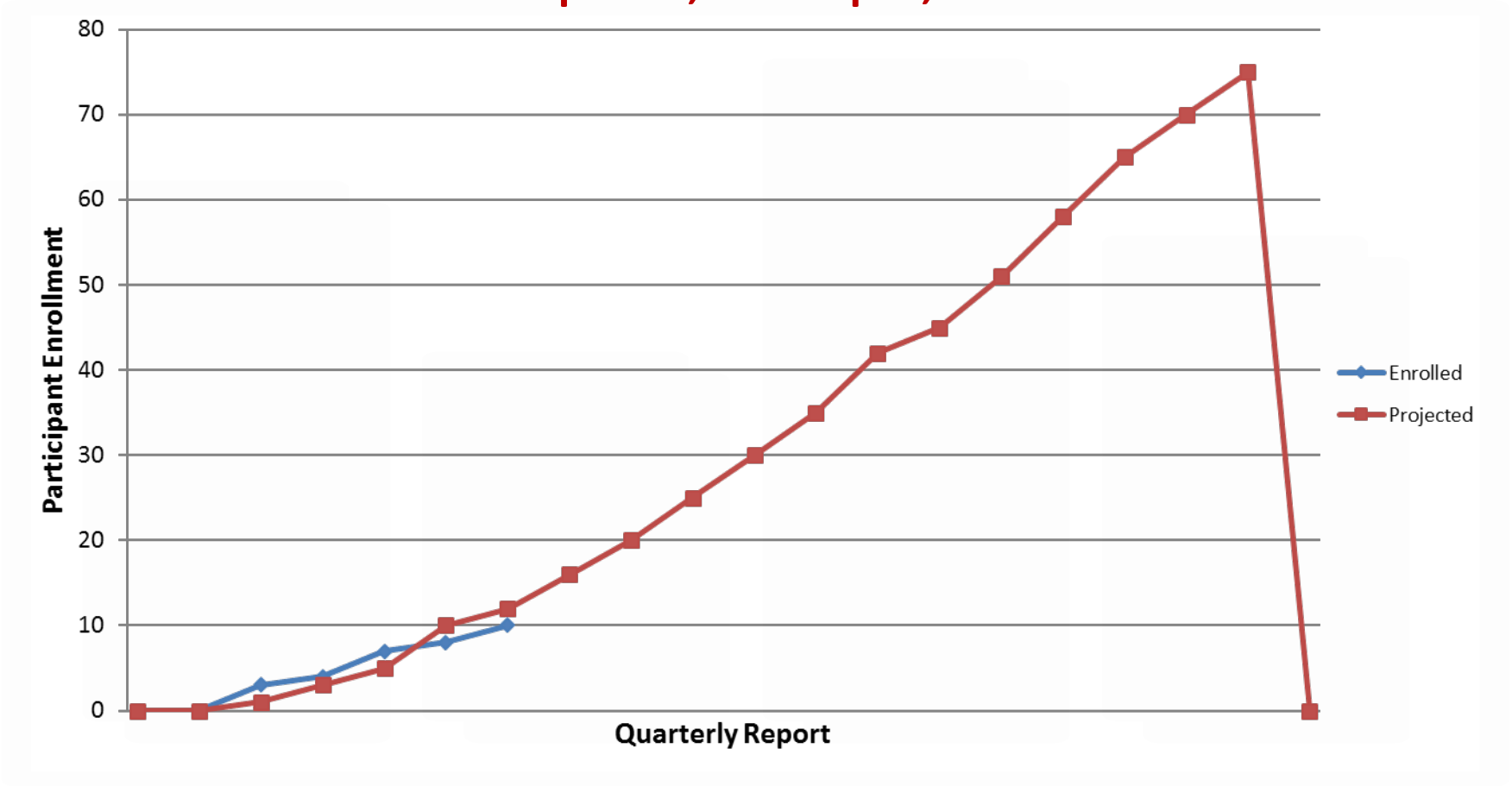


Percent of participants that have completed the study	**0%**

CONSORT Diagram – UT Dallas, Dallas, TX

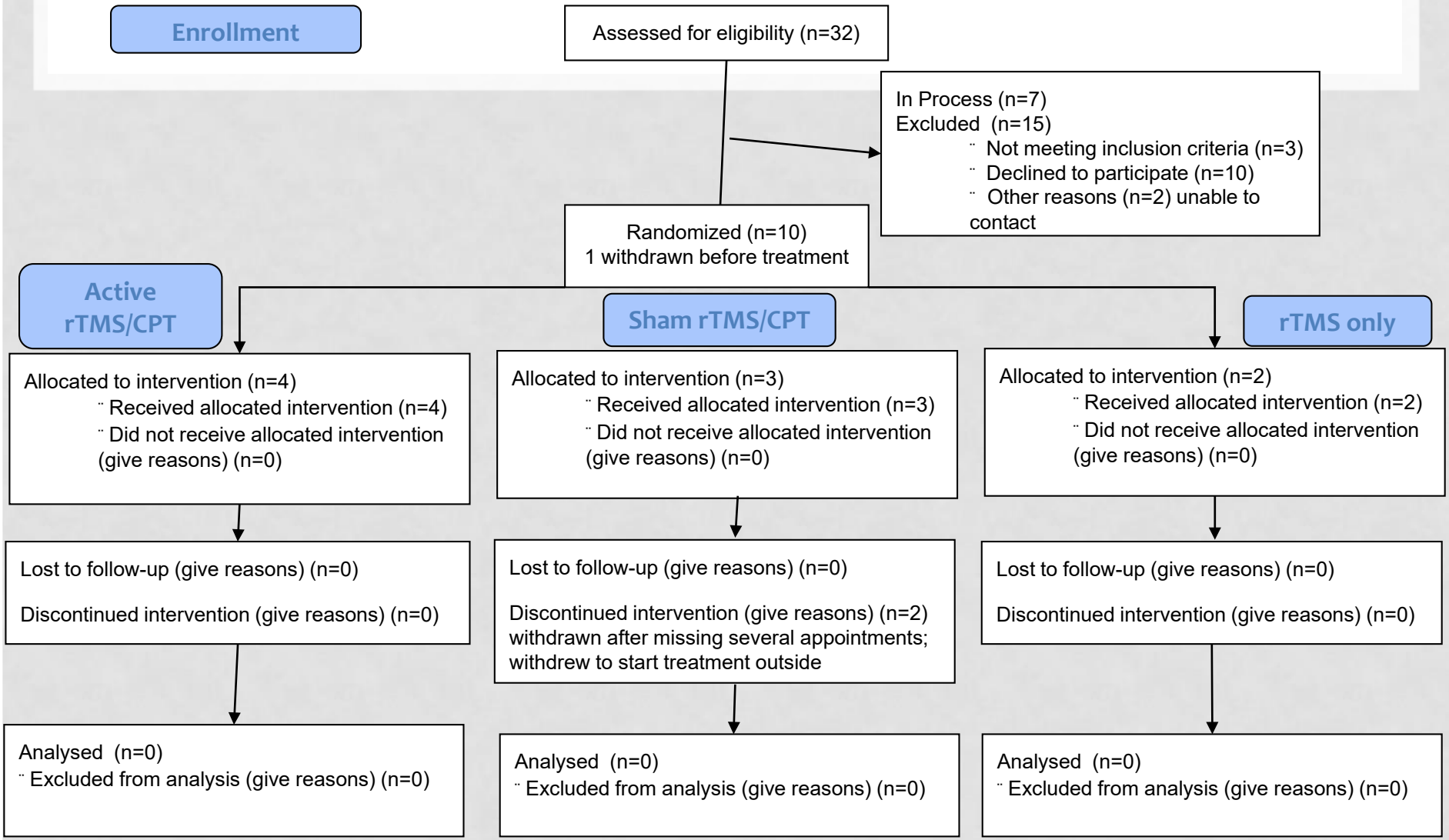


Recruitment and Retention – James A. Haley VA Hospital, Tampa, FL

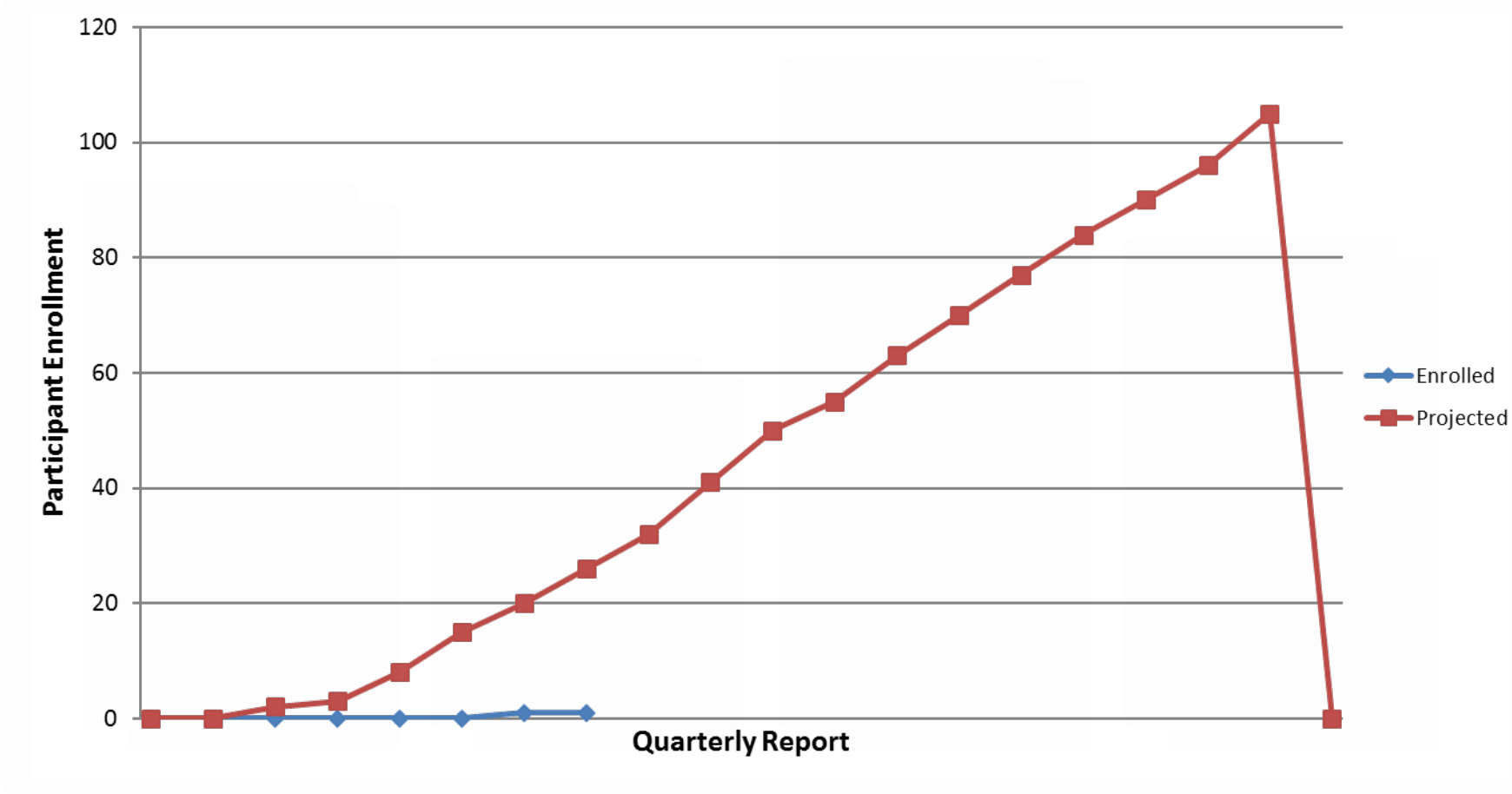


Percent of participants that have completed the study	**0%**

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