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TITLE: Transcranial Magnetic Stimulation of the Default Mode Network to Improve Sleep

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Abstract:

The present study will investigate the efficacy of a non-pharmacological method of alleviating insomnia by administering both continuous theta burst (cTBS) transcranial magnetic stimulation (TMS) and sham to 20 volunteers (aged 20-40) with self-reported sleep problems. This study will employ a counterbalanced, double-blind crossover study design. It is hypothesized that cTBS administered to a node of the default mode network (DMN) shortly before bed will decrease rumination and facilitate a faster transition from wakefulness to sleep. Anatomical and functional MR imaging data, as well as spectroscopy, will be collected pre- and post-stimulation in order to detect changes in connectivity and chemical composition. Cognitive- and attention-based tasks will be used to characterize changes in cognitive functioning prior to stimulation, immediately after stimulation, and following a night of sleep. We will employ polysomnography and actigraphic sleep monitoring to evaluate sleep quality, latency, and duration.

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1. INTRODUCTION:

The present study will investigate the efficacy of a non-pharmacological method of alleviating insomnia by administering both continuous theta burst (cTBS) transcranial magnetic stimulation (TMS) and sham to 20 volunteers (aged 20-40) with self-reported sleep problems. It is hypothesized that a mild disruption of default mode network (DMN) activation prior to sleep will lead to 1) decreased resting state functional connectivity within the DMN; 2) increased gamma-aminobutyric acid (GABA) within the medial prefrontal cortical region of the DMN as measured using proton magnetic resonance spectroscopy (1H-MRS); 3) improved sleep (i.e., reduced sleep onset latency, wake after sleep onset, and number of awakenings; and increased total sleep time, sleep efficiency, and a greater percentage of time in slow wave sleep); and 4) changes in connectivity and neurochemistry will correlate with improved sleep metrics and post-sleep cognitive performance. To test these hypotheses, we will stimulate a node of the DMN approximately two hours before bedtime using a transcranial magnetic stimulation (TMS) technique known as continuous theta burst (cTBS), which can reduce activation and connectivity within stimulated regions.

2. KEYWORDS:

Transcranial magnetic stimulation, insomnia, default mode network, continuous theta burst stimulation

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim 1: Determine the effects of cTBS targeted to the DMN on sleep quality, brain neurochemistry, functional connectivity, and next-day cognitive performance.

- **Major Task 1:** Obtain IRB/HRPO approval, hire staff, and procure equipment
  - **Subtask 1:** Prepare regulatory documents and research protocol
    - Refine eligibility criteria, exclusion criteria, and screening protocol **(completed 7/27/20)**
    - Finalize consent form and human subjects protocol **(completed 7/27/20)**
    - Submit protocol for local UA IRB Review **(completed 9/08/2020)**
    - Submit protocol for Military 2nd level IRB review (ORP/HRPO) **(completed 9/30/20)**
    - Submit amendments, adverse events and protocol deviations as needed **(ongoing, latest amendment submitted 08/13/2021)**
    - Complete annual IRB/HRPO continuing review report **(latest IRB continuing review submitted 7/26/21, approved 08/11/21)**

    - **Subtask 2**: Hire Staff and Acquire Testing Materials
        - Train research staff on study-related protocols **(100% complete)**
        - Acquire and organize research materials and equipment **(100% complete)**
        - Perform test runs of data collection activities to refine and perfect data collection protocols and procedures **(completed 09/13/21)**
- **Major Task 2**:
    - **Subtask 1**: Collect data for n=20 participants (10 male, 10 female)
        - Place advertisements for participant recruitment **(began 08/04/2021, ongoing)**
        - Prescreen and determine eligibility for all interested potential participants **(began 08/04/2021, ongoing)**
        - Enroll and run eligible subjects through all study activities **(begins 09/09/2021)**
        - Clean, score, process, and prepare data for analysis (**begins 09/09/2021)**
- **Major Task 3:** Analyze data and disseminate results
    - **Subtask 1**: Perform statistical analyses
        - Conduct statistical analyses of data using SPSS
    - **Subtask 2**: Publish findings and submit final report
        - Submit abstracts and manuscripts for publication
        - Prepare final report describing study findings

What was accomplished under these goals?

During the past annual reporting period, we have taken the study from the planning stages to the active recruitment stage. All regulatory processes, including IRB and HRPO approvals, have been completed. We have trained six undergraduate students, two full-time research technicians, and one doctoral-level research scientist on recruitment, enrollment, and data collection activities. As the school year begins, additional undergraduate students are being trained on the aforementioned duties. We have generated all study tasks, pilot-tested all aspects of the study, and procured all materials required to conduct data collection activities.

We have begun recruiting through a variety of recruitment avenues and have received an influx of initial interest.

Our study recruitment progress is described below:

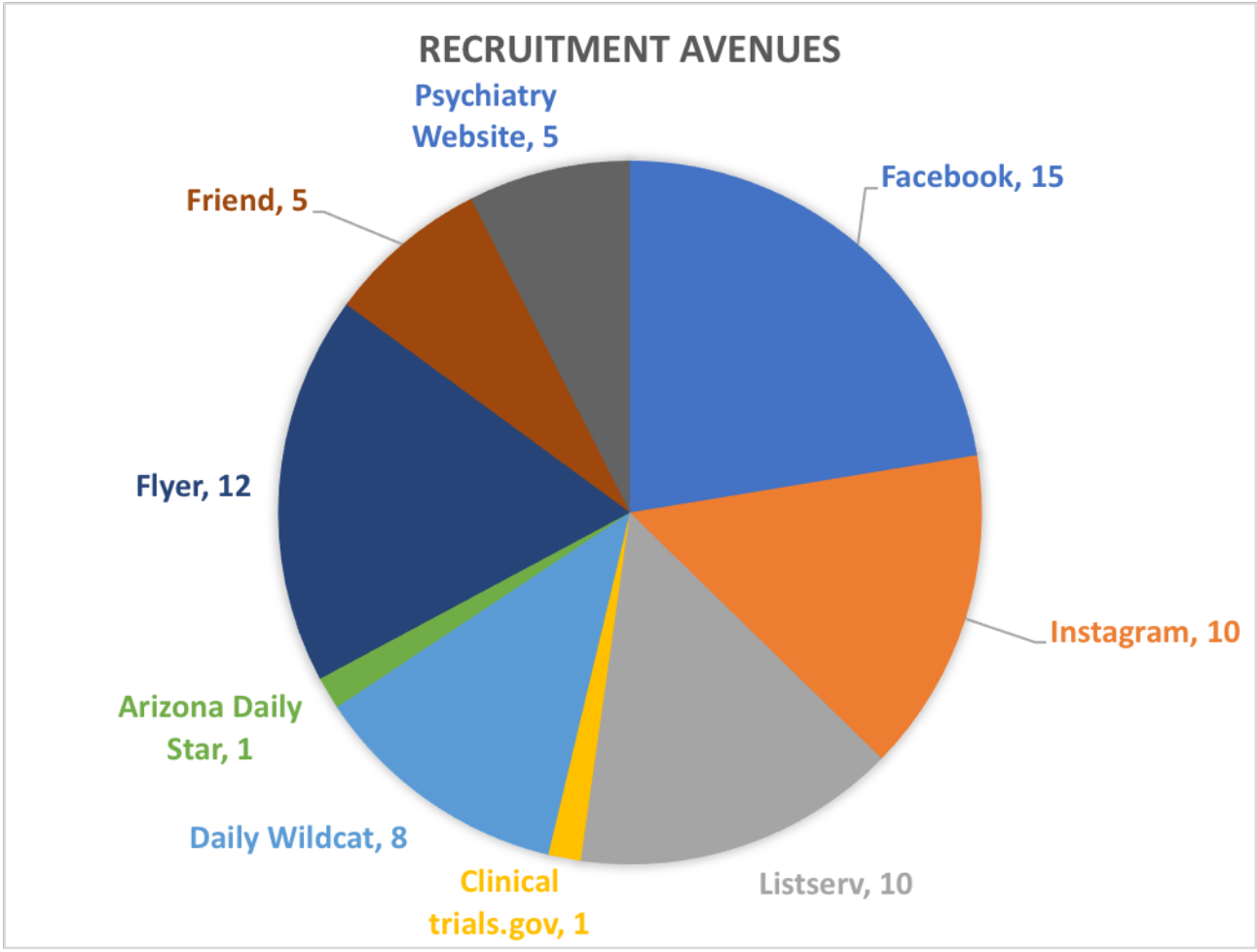

Figure 1: Number of individuals who learned about our study through our various recruitment avenues.

As of Aug. 31st, 2021, our most successful recruitment method has been Facebook with 15 individuals who expressed interest. 12 individuals heard about our study from flyers posted in local businesses in the Tucson metro area, 10 individuals heard about the study from online ads posted through Instagram, 10 individuals heard about the study from University of Arizona Listservs (i.e. email blasts sent through various departments and organizations), and 8 individuals heard about the study from the University of Arizona student newspaper, the Daily Wildcat. The remaining individuals heard about the study via word of mouth, web searches, or the Arizona Daily Star.

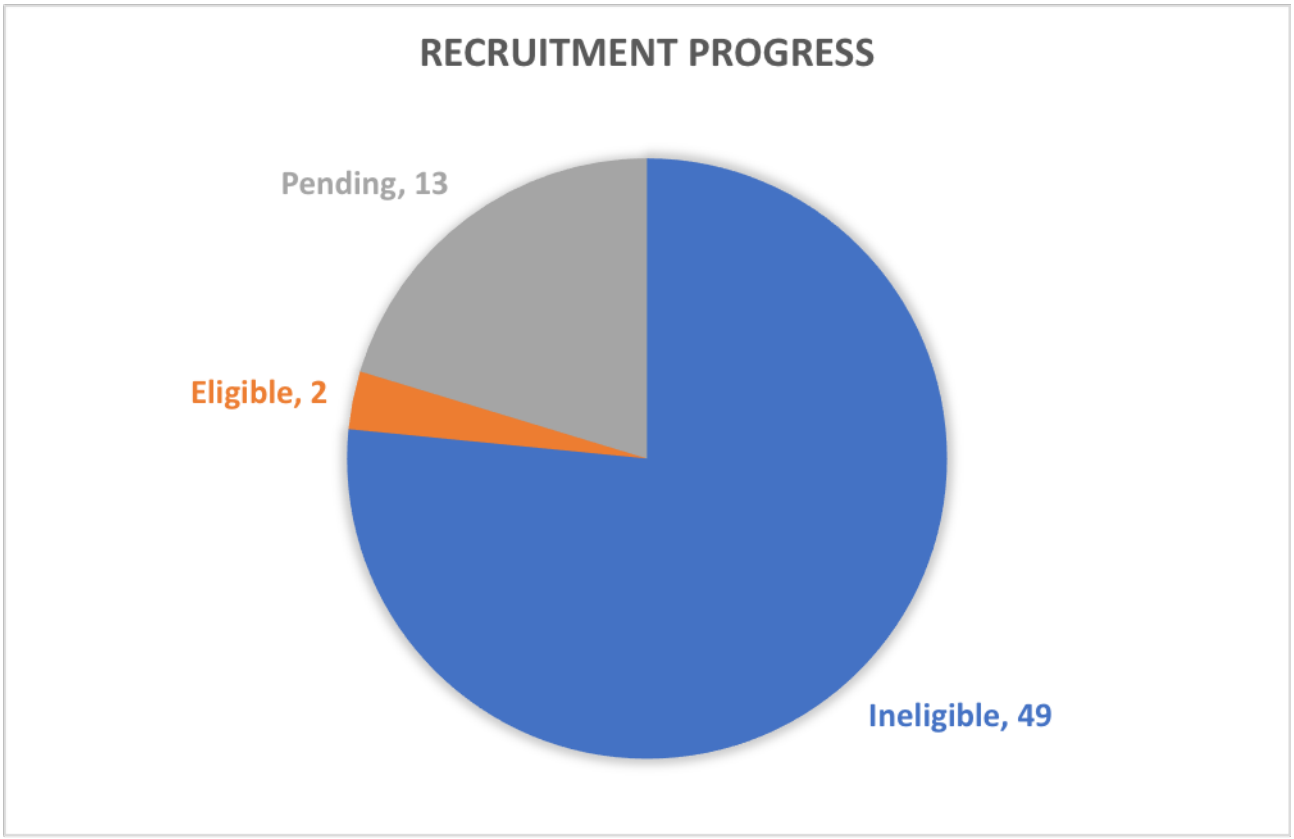

Figure 2: Breakdown of recruitment progress as of the end of this reporting period.

As shown in Figure 2, a total of 64 individuals have expressed interest in participating. Of these individuals, 2 were eligible after initial screening and were subsequently scheduled for enrollment visits to take place in September, 49 were ineligible after initial screening, 0 were lost to follow-up, and 13 were pending an eligibility decision as of 08/31/2021 (this category includes individuals who have contacted the team to express interest in the study, but have not yet completed the online screening form).

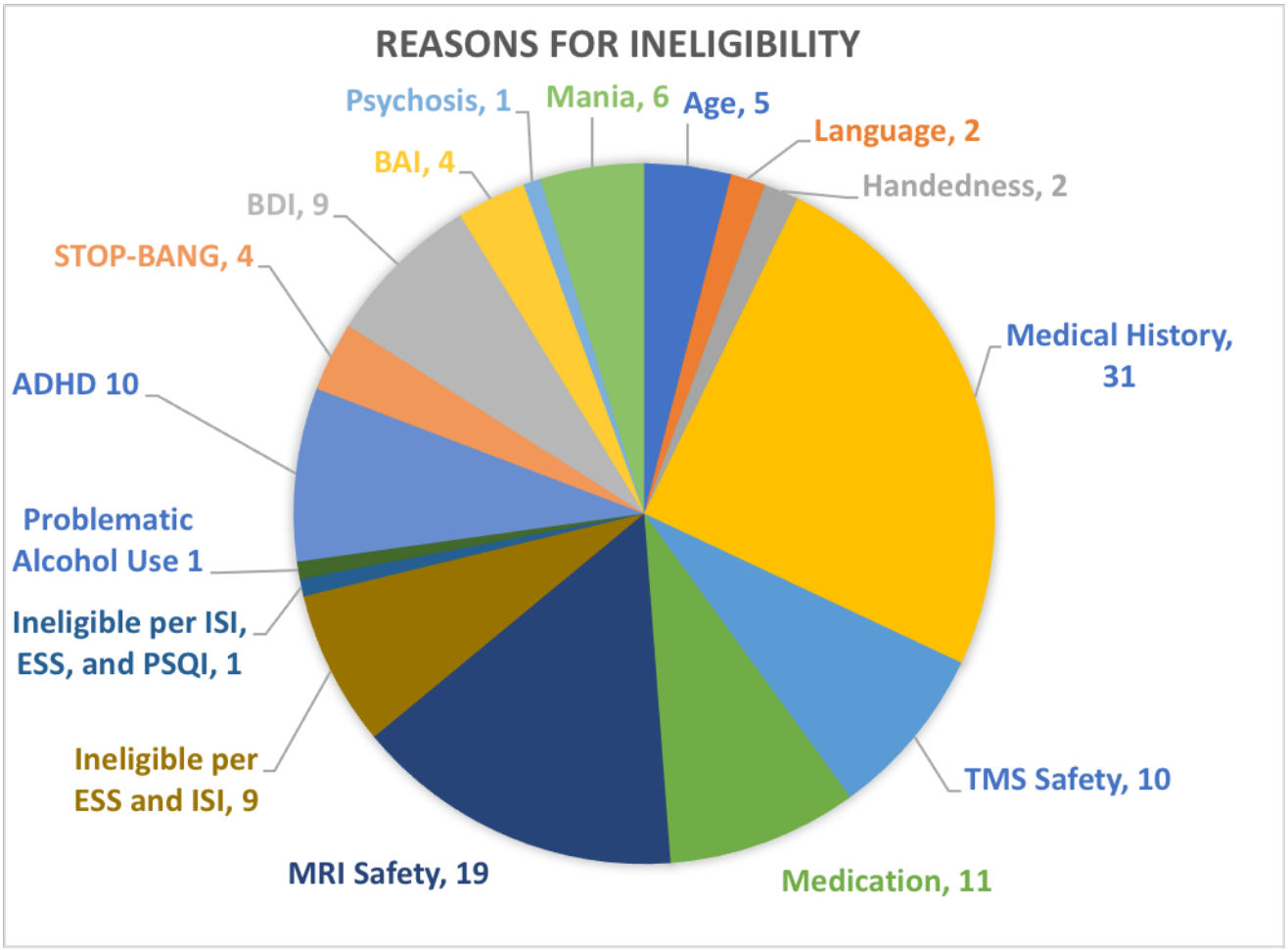

Figure 3: Exclusion factors for the 49 ineligible individuals as of 08/31/2021. ESS=Epworth Sleepiness Scale, ISI=Insomnia Severity Index, PSQI=Pittsburgh Sleep Quality Index, STOP-BANG=Snoring, Tired, Observed, Pressure, Body Mass Index, Age, Neck size, Gender (an obstructive sleep apnea risk assessment), BDI=Beck Depression Inventory 2nd edition, BAI=Beck Anxiety Inventory. ADHD symptoms are assessed using the Adult ADHD Self-Report Scale (ASRS-v1.1). Psychosis and mania symptoms are assessed using questions from the Mini-International Neuropsychiatric Interview (MINI) version 6.0.0.

Figure 3 shows the exclusion factors for our 49 ineligible individuals to-date. These individuals have been excluded for reasons related to safety (e.g. metal in the body, history of seizures) or data validity (e.g. left handedness, no current insomnia). The majority of ineligible individuals were ineligible for multiple reasons (e.g. left-handed, permanent retainer); as such, the total count of exclusionary factors exceeds the number of ineligible people. Medical history (e.g. brain tumors, nicotine use) has ruled out the greatest number of individuals.

What opportunities for training and professional development has the project provided?

Three research personnel worked closely with Dr. Chou's team to gain proficiency in TMS administration. Two research personnel worked closely with the study coordinator to train in PSG electrode application. In total, 9 research personnel, including undergraduate research assistants, have been trained on various aspects of the study, including eligibility screening, neuropsychiatric assessments, and sleep monitoring.

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 have several study visits scheduled for the next quarter and we continue to receive a steady stream of interest in our study. In the next reporting period, we plan to continue evaluating our recruitment methods and adjusting as necessary to obtain optimal rates of recruitment and meet our goal sample size. Additionally, we plan to clean and conduct preliminary analyses with study data as it is collected in order to report preliminary findings.

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?
Nothing to report.

5. CHANGES/PROBLEMS:
Changes in approach and reasons for change

Item	Type of amendment	UA IRB Submission	UA IRB Approval Date	UA IRB Approval Submitted to HRPO	Approved by HRPO
New Project Initial Approval	New project	7/27/2020	9/28/2020	eBRAP	3/30/2021
Amendment # 1: Study personnel update, new recruitment ads.	Minor	3/2/2021	3/19/2021	N/A	N/A

Add perfusion scan to measure blood flow pre- and post-TMS. Revise consent to request permission to contact for future research. Removed recruitment of military personnel. Add Google Voice for correspondence with subjects and Qualtrics data collection.					
Amendment # 2: Revised cTB stimulation intensity from 80% active motor threshold (AMT) to 70% resting motor threshold (RMT)as a likely more appropriate determination of stimulation intensity. Add Pre- and post-TMS symptom assessment to monitor for adverse effects. Revised exclusion criteria for alcohol use to >14 drinks per week for males and >7 drinks per week for females. Added Alcohol Use Disorders Identification Test (AUDIT) to assess alcohol use and vital sign measurements to better ensure subject safety.	Minor	4/19/2021	5/18/2021	N/A	N/A

Amendment #3: Removed IAPS task and PVT from enrollment visit, minor wording changes to questionnaires for clarity. Changed instructions for arriving to visits due to changes in building security due to COVID. Allowed visits to take place on any day of the week. Personnel changes.	Minor	5/25/2021	6/18/2021	N/A	N/A
Amendment #4: Removed VAT task, added additional spectroscopy scan, added recruitment material. Personnel changes. Minor subject material changes (e.g. provided updated COVID guidance, clarified where to meet for scheduled visits).	Minor	8/13/2021	8/24/2021	N/A	N/A

Actual or anticipated problems or delays and actions or plans to resolve them

While many COVID-19 restrictions have been lifted and local rates of vaccination continue to rise, it is possible that viral variants and spikes in transmission may influence recruitment and research activities in future reporting periods. Our lab will continue to adhere to applicable guidance and adapt our operations as necessary.

While initial interest in our study has been high, our safety-related exclusionary criteria for MRI and TMS have ruled out many interested individuals. As such, we will continue to monitor the recruitment progress over the coming reporting periods and if necessary, we may alter our exclusionary criteria for non-safety-related conditions to boost enrollment. For example, we may opt to include individuals who self-report a depression and/or anxiety diagnosis in the past two years, but who currently do not demonstrate moderate-to-severe

symptoms per the BDI or BAI. We will continue to work closely with our expert collaborators in TMS to ensure that any changes made will not significantly impact participant safety or data quality.

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**
  Nothing to report.

- **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

Name: Dr. William “Scott” Killgore
Project Role: Principal investigator
Nearest person month worked: 0.420
Contribution to project: Dr. Killgore oversaw all study activities, including MRI parameter development, the IRB amendment, and staff training.

Name: Dr. Natalie Dailey
Project Role: Co-investigator
Nearest person month worked: 0.300
Contribution to project: Dr. Dailey assisted with research personnel training efforts, computerized task development, and MRI parameter development.

Name: Dr. Ying Hui Chou
Project Role: Co-investigator
Nearest person month worked: 0.360
Contribution to project: Dr. Chou assisted with research personnel training efforts for transcranial magnetic stimulation (TMS).

Name: Dr. Yu-Chin Chen
Project Role: Graduate student
Nearest person month worked: 0.720
Contribution to project: Dr. Chen assisted with research personnel training efforts for transcranial magnetic stimulation (TMS).

Name: Ayla Bullock
Project Role: Primary coordinator
Nearest person month worked: 1.560
Contribution to project: Ms. Bullock coordinated research personnel training, communicated with collaborators, developed materials for the IRB amendment, and generated SOPs and study materials.

Name: Samantha Jankowski
Project Role: Student research technician
Nearest person month worked: 2.400
Contribution to project: Ms. Jankowski trained on all study protocols and assisted Ms. Bullock with developing study materials.

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: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ebrap.org/eBRAP/public/index.htm*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil/Pages/Resources.aspx) should be updated and submitted with attachments.*

9. APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.