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TITLE: Hyperbaric Oxygen therapy in the Treatment of Chronic Mild-Moderate Blast-Induced Traumatic Brain Injury PCS and PTSD

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The purpose of the study is to see if an eight-week course of forty low-pressure HBOT's can significantly improve symptoms and cognitive function in military veterans and civilians with mild TBI/PPCS. The proposed design is a randomized controlled (non-treatment, non-sham) single-arm crossover single-blind study. The scope of the project is to recruit, enroll, test, treat, re-test and follow-up on 50 subjects at Louisiana State University, New Orleans in 23 months and another 50 subjects at Oklahoma State University in an equivalent period of time. The study received final approval from all regulatory agencies on 5/13/2014. Enrollment began shortly thereafter. By 9/30/2015 88 subjects had been screened, 29 subjects have been enrolled, and five of these have withdrawn, leaving a total of 24 enrolled. Twelve subjects have completed the protocol. Four were in treatment at the end of September, one was in the control period, and 7 are in the two-month follow-up period post-hyperbaric oxygen treatment. Four additional subjects have been screened in October 2015 and nine are awaiting first appointment for enrollment. The second site for the study, Oklahoma State University Center for Health Sciences, has not participated in the study due to inability to secure funding. There are no study results to report at this time and no significant adverse advents. The study is on temporary hold due to an interim review by the LSUHSC-NO IRB. The review has been completed and it is expected the hold will be released in November 2015.

15. SUBJECT TERMS

HBOT: hyperbaric oxygen therapy; TBI: traumatic brain injury; PPCS: persistent post-concussion syndrome

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I. INTRODUCTION

Mild-moderate blast-induced traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) affect 11-28% and 13-17%, respectively, of U.S. combat troops returning from Iraq and Afghanistan. Mild TBI affects another 2 million civilians in the United States and far greater numbers worldwide. Approximately 10-15% of mild TBI patients experience the persistent post-concussion syndrome (PPCS). Evidence-based medicine exists for PTSD, but there is no effective treatment for the persistent post-concussion syndrome (PPCS) of mild-moderate TBI nor the combined diagnoses of PPCS and PTSD. Between the Fall of 2008 and end of 2010, the P.I. conducted a non-controlled pilot trial of hyperbaric oxygen therapy (HBOT 1.5 atmospheres absolute/60 minutes, twice/day, 40 treatments in one month) in military veterans with both TBI/PPCS and PTSD that achieved substantial symptomatic, cognitive, and brain imaging improvements in the subjects. Preliminary results were published 11/2011 in the Journal of Neurotrauma (http://www.liebertonline.com/doi/abs/10.1089/neu.2011 .1895). The original purpose of the present study was to replicate the pilot trial in a randomized sham-controlled double-blind design with the sham-control group receiving slightly pressurized air at the beginning and end of each treatment. After further review of the science and discussion with the FDA the study was changed to: 1) a randomized controlled (non-treatment non-sham) single-arm crossover single-blind design, 2) include both military and civilian subjects with the single diagnosis of PPCS from either blast or blunt trauma, and 3) an eight week course of treatment, instead of four weeks.

Therefore, the purpose of the new proposed study is to see if an eight-week course of forty low-pressure HBOT's can significantly improve symptoms and cognitive function in military veterans and civilians with mild TBI/PPCS using a randomized controlled single-arm crossover design. The scope of the project is to recruit, enroll, treat, test, retest, and follow-up test 50 subjects within 23 months at LSU, New Orleans and another 50 subjects at Oklahoma State University Health Sciences Center, Tulsa, Oklahoma.

To date the University of Oklahoma researchers has not been able to secure funding for their half of the study.

II. BODY

The research accomplishments associated with the tasks in the Statement of Work of 12/18/2013 are as follows:

A. Obtain TATRC IRB and scientific reviews/approvals: IRB approval was obtained from LSU School of Medicine 12/18/2013. Second level (final) ORP approval was obtained on 5/13/2014. VA IRB submission was planned after ORP approval, but abandoned due to the high probability of inestimable further delays as described in previous reports.

B. Recruit sufficient numbers of appropriate subjects to complete the study within project period: The rapid approval by ORP was followed by local CBS television airing in early June, 2014. Granting of a No Cost Extension allowed relaxation of a very optimistic recruitment expectation in the Year 4 First Quarter Report (April, 2014). Recruitment proceeded through the end of August on target, during which time email, phone advertising and announcement, website posting, and contact with all sources mentioned in the 12/18/2013 SOW occurred. Despite this effort enrollment slowed in late August and early September, 2014. Billboard posting and direct mailing ensued. The first subject was enrolled on 8/8/2014. By 12/31/2014 nine subjects had been enrolled, 8 additional subjects were enrolled in each of the first two quarters of 2015, and 4 subjects in the third quarter for a total of 29. Seven of these subjects were enrolled from 5/2014 to 9/30/2014 and the remaining twenty-two subjects enrolled in the past year since 9/30/2014. Five of these 29 subjects have withdrawn, leaving 24 subjects total enrolled in the study. The pace of screening was sustained in the 4th quarter of this last year, however a higher percentage of screened patients did not meet criteria for enrollment.

Twelve subjects have completed the protocol. Four were in treatment at the end of September, one was in the control period, and 7 are in the two-month follow-up period post-hyperbaric oxygen treatment. Nine additional subjects have been screened and are awaiting first appointment for enrollment. Their enrollment has been delayed by a hold placed on the study on 9/25/2015 by the LSUHSC-NO IRB for a mid-study review. This review has been completed and removal of the study hold should occur in November. Despite the hold we should be able to continue the pace of 2-3 enrolled subjects/month. The P.I. had expected increased enrollment in the 4th Quarter from VA referrals based on a local policy change allowing VA advertising for non-VA-approved studies in 3/2015. Unfortunately, to this date the final approval of this study for VA posting has not occurred and the VA has not referred any subjects.

At the present enrollment pace the study will need a No Cost Extension until the end of 2016 to complete the study at LSU. Inquiry regarding an NCE was made in August 2015 and will be formalized in the near future. Meanwhile, co-researchers at Oklahoma State University Center for Health Sciences have been unable to secure funding for their half of the study. Pre-application was

submitted and declined. There are currently no prospects to secure funding in the future.

C. Enroll, test, and treat 50 subjects within 17 months from award date: Based on the final ORP approval date of 5/13/2014 and the current pace of enrollment the study should be completed in 12/2016. To do so will require a No-Cost-Extension from the current date of 3/28/2016. Tasks 3.a.-f. in the Statement Of Work have not changed. Each subject is adhering to this schedule. They are renumbered C.1-6 with appropriate change of dates:

1. Recruit subjects, beginning the end of May 2014. Patients in the HBOT Group will complete the protocol in 18 weeks while patients in the Control Group will complete the protocol in 27 weeks.

2. Obtain consent, take hyperbaric medicine history, and conduct physical exam at the hyperbaric facility (Family Physicians Center) and additional study site. This subtask will be completed during the week of recruitment, most likely on the day the subject is recruited.

3. Perform psychometric testing and questionnaires at Neuro-psychological and Psychological Services for Children and Adults, LLC, 2626 N. Arnoult Rd, Ste 220, Metairie, LA, which is 10 miles from the hyperbaric facility. The collaborator performing this task is Dr. Susan Andrews. This task will be accomplished during the first week of re-cruitment, most likely on the second day. The same task will be com-pleted at the second study site on the same timeline.

4. Post-treatment physical exam conducted by the PI at the hyperbaric facility on or about the day of the 40th hyperbaric treatment.

5. Repeat psychometric testing and questionnaire completion by Dr. Andrews the day following the 40th hyperbaric treatment.

6. Repeat NSI and QOLIBRI eight weeks following the 40th hyperbaric treatment.

D. Analyze data and submit a manuscript for peer-reviewed publication within 24 months of funding and within 8 months of completion of the study: Given the timeline in C. a more accurate statement of this goal would be a publication by August, 2017, assuming a No-Cost-Extension can be obtained through 12/2016.

III. KEY RESEARCH ACCOMPLISHMENTS

The key research accomplishment is the enrollment of 24 subjects by 9/30/2015

without any significant adverse events.

IV. REPORTABLE OUTCOMES

There are no reportable outcomes. No data has been analyzed.

V. CONCLUSION

The study is actively recruiting. Twenty-four subjects have been enrolled, 12 have completed the study, and an additional nine subjects are awaiting the final screening neuropsychological appointment. The study is on hold since 9/25/2015 for an interim review by LSUHSC-NO IRB which should be released in November 2015.

VI. REFERENCES

There are no references.

VII. APPENDICES

There are no appendices.

VIII. SUPPORTING DATA

There is no supporting data.