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TITLE: Phase 2 Randomized Controlled Trial of Sildenafil Citrate for Treatment of Cerebrovascular Dysfunction in Chronic Traumatic Brain Injury

PRINCIPAL INVESTIGATOR: Ramon Diaz-Arrastia, MD, PhD

CONTRACTING ORGANIZATION: University of Pennsylvania, Philadelphia, PA

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Phase 2 Randomized Controlled Trial of Sildenafil Citrate for Treatment of Cerebrovascular Dysfunction in Chronic Traumatic Brain Injury

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Ramon Diaz-Arrastia, MD, PhD

E-Mail: Ramon.Diaz-Arrastia@pennmedicine.upenn.edu

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5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Pennsylvania
Department of Neurology
3400 Spruce Street
Philadelphia, PA 19104

8. PERFORMING ORGANIZATION REPORT NUMBER

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The failure of multiple clinical trials for traumatic brain injury (TBI) highlight the urgent need for biomarker-driven strategies to identify specific brain pathologies and provide an objective measure to monitor pharmacodynamics and evaluate therapeutic efficacy. This project builds on our Phase IIa study of a phosphodiesterase 5 (PDE5) inhibitor, sildenafil citrate, in chronic TBI (ClinicalTrials.gov NCT01762475). We demonstrated that: (1) CVR is decreased in patients with chronic TBI; (2) sildenafil improves CVR in these patients; and (3) 8-week treatment with sildenafil citrate, at 25 mg twice daily, was well tolerated and associated with a trend towards clinical improvement. This Phase IIb trial will extend these findings by identifying the optimal effective and tolerated dose, fine tune study procedures and inclusion/exclusion criteria, and further assess the effect of sildenafil on post-TBI symptoms and cognitive function. Over the first year of this project we have completed all the regulatory requirements to launch the project, including IRB and OHRO approval, have hired and trained research staff, purchased investigational product and manufactured placebo tablets, finalized the protocol, manual of operations, analytical plan, and pharmacy manual.

15. SUBJECT TERMS
None listed.

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

TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

The failure of multiple Phase III clinical trials of therapies known to be effective in animals has forced a re-evaluation of clinical studies in traumatic brain injury (TBI). Multiple NIH and DoD expert panels over the past 10 years highlight the urgent need for biomarker-driven strategies to identify subgroups of TBI patients with specific brain pathologies, confirm that therapy is engaging the proposed molecular target, and provide an objective measure to monitor pharmacodynamics and evaluate therapeutic efficacy. This proposal adheres to these recommendations by targeting a common endophenotype of TBI, traumatic cerebrovascular injury (TCVI), and using an imaging biomarker, cerebrovascular reactivity (CVR), to confirm target engagement, optimize dose, and assess physiologic efficacy. It builds on our prior Phase IIa study of a phosphodiesterase 5 (PDE5) inhibitor, sildenafil citrate, in chronic moderate-to-severe TBI patients (ClinicalTrials.gov NCT01762475). We demonstrated that: (1) CVR is decreased in patients with chronic TBI; (2) sildenafil improves CVR in these patients; and (3) 8-week treatment with sildenafil citrate, at 25 mg twice daily, was well tolerated and associated with a trend towards improvement in neuropsychological symptoms.11 This Phase IIb trial will lay the foundation for the design of a future definitive Phase III which will definitively test the efficacy of sildenafil on a clinically meaningful outcome measure in patients with chronic TBI.
The major goals of this study is to carry out a Phase 2b clinical trial including a 4-week, placebo-controlled, double-masked dose finding and safety-tolerability study of approximately 160 participants with chronic TBI more than 6 months prior to enrollment and who remain symptomatic and disabled with the following study aims:
Aim 1 (Primary Aim- Pharmacodynamic): To determine the optimal PDE5 inhibitor dose to improve microvascular function (ΔCVR measures) after a single PDE5 inhibitor dose.
Aim 2 (Primary Aim- Safety and Tolerability): To assess the safety and tolerability of a range of PDE5 inhibitor doses in chronic moderate-severe TBI subjects.
Aim 3 (Secondary/Exploratory Aim): To measure the effect of chronic (4-week) P PDE-5 inhibitor administration at 3 different doses on TBI symptom self-report and functional outcome measures.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Chronic traumatic brain injury; traumatic microvascular injury; cerebrovascular reactivity; nitric oxide; phosphodiesterase 5; sildenafil citrate; Glasgow Outcome Scale-Extended; Cognitive function; Executive function; neuropsychological testing; neuropsychologic symptoms; headache impact test;

3. ACCOMPLISHMENTS: *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

The major goals of this study is to carry out a Phase IIb clinical trial including a 4-week, placebo-controlled, double-masked dose finding and safety-tolerability study of approximately 160 participants with chronic TBI more than 6 months prior to enrollment and who remain symptomatic and disabled with the following study aims:

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Aim 3 (Secondary/Exploratory Aim): To measure the effect of chronic (4-week) PDE-5 inhibitor administration at 3 different doses on TBI symptom self-report and functional outcome measures.

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

During the first year of work on this project, the following has been accomplished:

1. Clinical Trial protocol and informed consent form were finalized. Eligibility criteria, exclusion criteria, and screening protocol were refined and finalized.
2. Neuropsychometric outcome battery was finalized.
3. IRB approval at the University of Pennsylvania (which will function as the central IRB for this study) was obtained.
4. Approval from DoD OHRO was obtained for enrollment at the University of Pennsylvania.
5. Subcontracts between the University of Pennsylvania, WRNMMC, and RTI International have been completed.
6. Ceding process from IRB at WRNMMC and Univ. of Pennsylvania is under way.
7. Clinical Research Coordinators to work on this project were hired at the University of Pennsylvania. Space allocation for these individuals was obtained.
8. Training of research staff on clinical protocol and hypercapnia MRI experiments is under way. Expect this to be finalized in November, 2023
9. Training of research staff on neuropsychometric assessments completed.

9. Training of research staff on neuropsychometric assessments completed.
10. RTI has completed the CRFs, and research database programming has been completed
11. ClinicalTrials.gov registration was completed.
12. Univ. of Pennsylvania Investigational Drug Services engaged in procuring active product (sildenafil citrate (Revatio®), 20 mg tablets, and preparation of placebo.
13. Pharmacy manual is has been completed.

Below the Milestones from the approved SOW are attached illustrating the progress that has been completed on this project.

	Time line (months)	USUHS/ NICoE	Penn	RTI	Status
Major Task 1: Protocol Preparation and Approvals					
Subtask 1: Prepare Regulatory Documents and Research Protocol for Study					
Coordinate CRADA with Penn, WRNMMC, and RTI	1-3	KW	RDA	TN	Complete
Establish DSA with WRNMMC and RTI	1-6	KW	RDA	TN	Complete
Refine eligibility criteria, exclusion criteria, screening protocol	1-3	KW	RDA		Complete
Finalize consent form & human subjects protocol	1-3	KW	RDA		Complete
Submit IRB protocol to WRNMMC IRB for Review	1-3	KW	RDA		Complete
HRPO Review of IRB documents	3-6	KW	RDA		Complete
Register study in ClinicalTrials.gov	3-6	KW	RDA	TN	Complete
Submit amendments, adverse events and protocol deviations prn	prn	KW	RDA		In progress
Submit annual IRB report for continuing review	Annual	KW	RDA		Complete for Year 1
Milestone Achieved: Penn IRB approval (Central IRB): Ceding approval WRNMMC IRB	6	KW	RDA		Complete
Milestone Achieved: All DUA/DSAs and CRADAs in place	6	KW	RDA	TN	Complete

Major Task 2: Coordinate Study Staff for Clinical Trial					
Subtask1: Hiring and Training of Study Staff					
Coordinate with Sites for job descriptions design	1-3	KW	RDA		Complete
Coordinate for space allocation for new staff	1-3	KW	RDA		Complete
Milestone Achieved: Research staff hired and trained	3	KW	RDA		Complete
Major Task 3: Randomized Controlled Trial					
Subtask 1: Study initiation visit and Launch RCT with full enrollment and data collection					
Study initiation visit	6	KW	Penn		Pending
Launch study and enroll/complete RCT in 15 subjects in year 1	6-12	KW	Penn		Pending

Participants will qualify for study based on inclusion/exclusion criteria outlined in the protocol. Summarizing, they will be between 18 – 55 years old, they will have experienced a TBI at least 6 months and no more than 10 years prior to enrollment; they must experience persistent post-concussive syndrome, and TBI-related disability (GOS-E 5-7).					
Enroll and complete RCT in 22 subjects in year 2	12-24	KW	Penn		Pending
Enroll and complete RCT in 22 subjects in year 3	24-36	KW	Penn		Pending
Enroll and complete RCT in 20 subjects in year 4	36-42	KW	Penn		Pending
Milestone Achieved: Intervention RCT completed on 160 eligible participants between two sited (Penn and NICoE)	6-42	KW	Penn		
Major Task 4: Aim 1 analysis: Imaging Data Analysis for optimal sildenafil dose					
Subtask 1: Data entry and analysis for assessment of optimal sildenafil dose to improve CVR in chronic TBI					
Coordinate CRFs and data management for the study	1-6	KW	RDA	TN	Complete
Finalize assessment measurements	1-3	KW	RDA	TN	Complete
Data entry with data verification	6-42	KW	RDA		Pending
Data entry complete on fully enrolled RCT and CVR data	42	KW	RDA		Pending
Data analysis and manuscript of imaging results submitted	42-48	KW	RDA	TN	Pending
Milestone Achieved: Database complete, locked and analyzed	48	KW	RDA		
Milestone Achieved: RCT and imaging results submitted to peer-review journal	48	KW	RDA	TN	
Major Task 5: Aim 2 analysis: Clinical Data Analysis for safety and tolerability					
Subtask 1: Data entry and analysis for assessment of sildenafil safety-tolerability across same dose range					
Coordinate CRFs and data management for the study	1-6	KW	RDA		Complete
Finalize assessment measurements	1-3	KW	RDA		Complete
Data entry with data verification	6-42	KW	RDA		Pending
Data entry complete on fully enrolled RCT and clinical data	42	KW	RDA		Pending
Data analysis and manuscript imaging results preparation/submission	42-48	KW	RDA	TN	Pending

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Drs. Diaz-Arrastia, Lippa, and Kenney met with our Lived Experience Consultant, Ms. Candace Gantt, during the development and finalization of the protocol, IRB submission, manual of operations. Ms. Gantt provided insights into the needs of the TBI stakeholder community, and provided suggestions on outreach to relevant communities and individuals who may be interested in participating in this study.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We will continue to meet on a quarterly basis with our Lived Experience Consultant, Ms. Candace Gantt. We also plan to add other members to our Lived Experience Consultant Panel. We will present this study to the Penn TBI Support Group, a group of TBI survivors and caregivers who meet monthly to learn about advances in TBI care and available resources in the community. Drs. Werner and Lippa will conduct similar outreach activities to the TBI clinic at Walter Reed National Military Medical Center and the National Intrepid Center of Excellence, once the study is open for enrollment at the Bethesda site.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report. This study is in the early stages.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report. This study is in the early stages.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report. This study is in the early stages.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report. This study is in the early stages.

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

There was unexpectedly high turnover or research staff both at the University of Pennsylvania and the Walter Reed National Military Medical Center. This required advertising, vetting, hiring, and training new research staff, which has been completed. This led to delays in finalizing the Protocol, Manual of Operations, and Pharmacy Manual. It also led to delays in finalizing the training of the research staff on MRI procedures and methods to measure cerebrovascular reactivity by administering hypercapnia.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

None. We have judiciously kept our expenditures under the projected budget as turnover in research staff led to delays in launching the study.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

None.

Significant changes in use or care of vertebrate animals

Not applicable. No vertebrate animals.

Significant changes in use of biohazards and/or select agents

Not applicable. No biohazards or select agents.

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

The scientific rationale and protocol for this study was published in an issue of *Neurotherapeutics* devoted to novel therapies for TBI.
The full citation is:
Kalyani P, Lippa SM, Werner JK, Amyot F, Moore CB, Kenney K, Diaz-Arrastia R. Phosphodiesterase-5 (PDE-5) Inhibitors as Therapy for Cerebrovascular Dysfunction in Chronic Traumatic Brain Injury. *Neurotherapeutics*. 2023 Sep 11. doi: 10.1007/s13311-023-01430-z. Epub ahead of print. PMID: 37697134.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

None.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

None

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

  None.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

  None.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

  None.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*

- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

None.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name: Ramon Diaz-Arrastia, MD, PhD
Project Role: Principal Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0001-6051-3594
Nearest person month worked: 1.0
Contribution to Project: Dr. Diaz-Arrastia has directly supervised Ms. Priyanka Kalyani, modifying and finalizing the protocol, preparing the informed consent form, arranging for IRB approval at the Univ. of Pennsylvania and OHRO. He has held bimonthly teleconferences with Drs. Kimbra Kenney, Sara Lippa, Franck Amyot, and Kent Werner at WRNMMC, as well as with Dr. Tracy Nolen at RTI. He has consulted with Ms. Candace Gannt, the Lived Experience Consultant on this project, and incorporated her advice on procedures for recruitment and retention. He hired Mr. Oli Zaff, who will be the Clinical Research Coordinator for this project, and has supervised his training.

Name: Priyanka Kalyani, MS
Project Role: Clinical Research Coordinator/Project Manager, Univ. of Pennsylvania
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 2 months
Contribution to Project: Ms. Priyanka Kalyani has been primarily responsible for preparing the study protocol, ICF, and OHRO submissions. She has been the direct contact with the University of Pennsylvania Investigational Drug Services.

Name: Pamela Bonner, MS
Project Role: Clinical Data Manager, RTI International
Researcher Identifier (e.g. ORCID ID)
Nearest person month worked: 3 months
Contribution to Project: Ms. Bonner worked directly under Dr. Nolen at RTI to develop the Case Report Forms and Research Database which will be used for this project.

Name: Carol Moore, MS
Project Role: Clinical Research Coordinator, Henry Jackson FOundation
Researcher Identifier (e.g. ORCID ID)
Nearest person month worked: 2 months
Contribution to Project: Ms. Moore worked directly under Drs. Werner, Kenney, and Lippa at WRNMMC to complete the regulatory requirements at WRNMMC and NICoE.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*

Nothing to report. No partner organizations other than those listed in the SOW and award.

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.*

Not applicable. Not a Collaborative 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.*

Quad Chart attached.

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.*

Attached is a .PDF of the published protocol paper:

Kalyani P, Lippa SM, Werner JK, Amyot F, Moore CB, Kenney K, Diaz-Arrastia R. Phosphodiesterase-5 (PDE-5) Inhibitors as Therapy for Cerebrovascular Dysfunction in Chronic Traumatic Brain Injury. Neurotherapeutics. 2023 Sep 11. doi: 10.1007/s13311-023-01430-z. Epub ahead of print. PMID: 37697134.