Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium

PASA Study Research Planning Program (SRPP)
Compound Development Research Grant Application
Request for Application (RFA) #4b: [FY19-Round 1]

Release: March 18, 2019

SUBMISSION AND REVIEW DATES

• Letter of Intent	13-May-19
• Full Application Deadline	22 -Jul-19
• Peer Review Process & Programmatic Review	16-Sep-19
• Notification of Award Recommendation	23-Sep-19
• Award Negotiations	07-Oct-19

Request for Application (RFA) #4b: [FY19-Round 1]
Synopsis

Full study implementation awards for proof-of-principle basic research to determine which compounds are most appropriate for human research trials.

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I. Funding Opportunity Description

A. Introduction

The Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium is funded by the Congressionally Directed Medical Research Programs (CDMRP) (http://cdmrp.army.mil/) as part of its Alcohol and Substance Abuse Disorders Research Program (ASADRP) from the FY14 and FY17 ASADRP consortium awards (W81XWH-14-ASARP-CA and W81XWH-17-ASADRP-CA). The PASA Consortium goal is to fund study applications for developing new medications that can be brought to therapeutic use to improve treatment outcomes for alcohol and substance use disorders (ASUD), especially as related to post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI). Studies of military and Veteran populations are encouraged. These medications will ideally address the comorbidity between ASUDs and PTSD or mild to moderate TBI because these comorbidities are common in a military population. Alcohol use disorder is the most common ASUD in the military, but opiate use disorder (OUD) also has developed significant clinical importance because of prolonged pain treatments with opiates. Because both ASUD and PTSD have FDA-approved pharmacotherapies, one logical starting point for treating this comorbidity might be to augment or combine these agents. The approved agents for ASUD are disulfiram, acamprosate, and naltrexone in either an oral and long-acting injection formulation. For OUD approved agents are methadone, buprenorphine, and naltrexone. For PTSD two serotonin reuptake inhibitors, sertraline (Zoloft®) and paroxetine (Paxil®), are FDA-approved pharmacotherapies. Although TBI is of interest, it has no FDA-approved specific pharmacotherapies, and none of these combined disorders have FDA-approved pharmacotherapies. Commercialization linked to FDA approval for these new medications or combinations of medications is critical so that early linkages to pharmaceutical companies are considered strengths of any application for PASA funding.

The medications listed above are examples only; the PASA SRPP is requesting applications for basic research to determine compounds to be used for treatment of any ASUD comorbid with PTSD or TBI most appropriate for future human research trials.

B. Program Description

The PASA Consortium is administered by a Management Core led by RTI International in collaboration with the Baylor College of Medicine (BCM). The PASA Consortium Leadership team consists of Principal Investigator Rick Williams, PhD, from RTI and co-Principal Investigators Tom Kosten, MD, from BCM and Tracy Nolen, DrPh, from RTI. Oversight of the Consortium is provided by a Government Steering Committee (GSC) assembled by the CDMRP.

The goal of the PASA Consortium is to fund study applications for developing new medications that can be brought to therapeutic use to improve treatment outcomes for ASUD, especially as related to PTSD and TBI. These medications will ideally address the comorbidity between ASUDs and PTSD or TBI.

C. The Management Core

The Management Core is responsible for soliciting and prioritizing applications. Successful applications will be selected by a GSC formed by the U.S. Department of Defense (DoD). The Management Core will provide oversight and coordination for future proof-of-principle basic research studies, receive all study data in a timely manner and act as a data repository, and provide analytic support in designing study randomization and performing statistical analyses. The Management Core will provide the administrative, protocol development and review, regulatory, statistical, resource, and data management/storage functions necessary to facilitate rapid development of research that would perhaps not otherwise be feasible without the Consortium approach. The Management Core contains

multidisciplinary expertise and experience in support of ASUD research. Additional information about PASA is available on its website: https://pasa.rti.org/.

II. Research Focus

A. Research Aim

The PASA Consortium has three broad aims:

1. Identify promising compounds,
2. Conduct proof-of-principle basic research to determine which compounds are most appropriate for human research trials, and
3. Conduct human proof-of-concept trials with promising compounds.

For this RFA, we are soliciting for research grants under basic science research studies (Aim 2). A separate RFA is available for planning grants for proof of concept human trials (Aim 2).

B. Basic Research

Discovery of new medications for ASUD comorbid with PTSD or TBI can greatly benefit from animal models of these disorders. Medications can be assessed to determine if they reduce the aberrant behaviors in models of ASUD comorbid with PTSD or TBI and potential dosages of these medications can be estimated for human studies. More importantly will be the interaction of substance intoxication or dependence with the PTSD or TBI models and the effect on the ASUD models after an animal has developed the aberrant behaviors of the PTSD or TBI models. PASA currently funds four basic research studies, details can be found here: https://pasa.rti.org/Research-Studies.

III. Submission Information

A. Types of Studies to be Awarded

Type	Period of Performance	Maximum Total Cost (Direct and Indirect)
Basic Research	18 months	$295,000

Note: ***Maximum total cost includes direct and indirect costs***. Deviations from these time and funding limits will require written permission from PASA Leadership. Please contact PASA_RFA@rti.org.

B. Application

All applications must include the following elements (as applicable) in the order as listed in this announcement. Page limits are noted where applicable. Failure to include a required element may result in the application not being reviewed. Start each component on a new page with the component title, PI name, and study title at the top of the first page.

Questions about the application process will be received until May 6, 2019, by e-mail to PASA_RFA@rti.org. Answers will be provided on a rolling basis, and just after May 6, 2019, the PASA Administrator will post on the PASA website a list of all the questions received along with the answers provided.

B.1 Letter of Intent

A letter of intent (LOI) must be submitted prior to submission of the full application. Early submission of the LOI will be greatly appreciated. The LOI shall not exceed four pages and provide:

- The title of the application;
- The name(s) and affiliation(s) of the PI and, if any, co-PIs;
- The address, phone number, and e-mail address of the PI;
- A brief overview of the study including research aims and objectives; and
- A list of the sites where the study will be conducted.

The LOIs are for planning purposes only and no response from the PASA Management Core is required to proceed with the full application. If any concerns or questions are identified upon review of the LOI, the PASA Management Core will contact the investigators to share that information.

B.2 Full Application Submission Requirements

All final applications must be submitted as a PDF file by e-mail no later than 11:59 PM Eastern Time on **July 15, 2019,** to:
PASA SRPP Administrator
PASA_RFA@rti.org

The full application consists of the following components:

Item	Description
Proposal Cover Sheet	See Appendix A for this template.
Title	Provide the title of the proposed project.
Study Personnel (3-page limit)	Demonstrate that the PIs, collaborators, and other researchers are well suited to the project and have an ongoing record of accomplishments. Describe any collaboration between civilian, DoD, or VA personnel. Include an organizational chart and briefly describe the roles and responsibilities of the study personnel.
Research Aims & Objectives (1-page limit)	Research aims and objectives should be clearly defined and sensibly tied to a definite research question. A clear endpoint or set of endpoints should be tied to each objective.
Study Rationale/Research Gap/Impact (1-page limit)	Projects should address an important problem or a critical barrier to progress in the field. The study should address an area of need targeted by the Consortium. All projects must be in line with PASA objectives and Aims. These Aims and priorities may change based on feedback from the GSC. The rationale should also clearly describe how the proposed study will align with DoD research and clinical goals to maximally benefit Service Members and Veterans.
Research Methods (10-page limit)	The overall strategy, methodology, statistical plan, and analyses should be well reasoned and appropriate to accomplish the specific aims of the project. A sample size estimate must be included and supported by a power analysis or other justification that demonstrates the adequacy of the sample size.
Innovation (1-page limit)	State how the project has the potential to significantly inform military or VA health care and practice. A successful proposal will also describe how the proposed research meaningfully expands on existing research without overlapping current studies or the unique contribution of the

Item	Description
	project to the research community and how it will not replicate current studies, but move beyond with an innovative approach or objectives.
Research Performance Sites (1-page limit)	Applicants should describe how the project benefits from unique features of the scientific environment, or collaborative arrangements. A description of all locations should also be provided. Also describe how each proposed site contributes to the study and how these sites will be able to complete the study protocol.
Management Core Collaboration (1-page limit)	The PASA Management Core should be meaningfully integrated into the research to support oversight and coordination, receive all study data in a timely manner and act as a data repository, and provide analytic support in designing study randomization and performing statistical analyses. The applicant should describe how the PI will integrate the proposed project with the existing PASA Management Core. A pre-submission teleconference between the PI and the Management Core to determine such arrangements can be requested.
Laboratory Animals (basic science studies only)	Each animal protocol must include (1) a justification for using animals, the number of animals to be used, and the species chosen; (2) the procedures or drugs to be used to eliminate or minimize pain and discomfort; (3) a description of the methods and sources used to search for alternatives to painful procedures; and (4) a description of the search used to ensure that the experiment does not unnecessarily duplicate previous research.
Research and Related Budget and Budget Justification	A budget justification which describes the labor and other direct costs necessary to complete the project must be included here. The budget should reflect yearly direct costs for each year over the entire period of performance. Because PASA project funding is available through a DoD award, all study subaward funds will be subject to policies and restrictions based on the DoD source of this funding. In addition, the full budget must be submitted on the form that will be available on the website: https://pasa.rti.org/About/Grant-Program
Quad Chart	All proposals must include a quad chart (separate from the proposal) briefly describing the study including rationale, population to be studied, sample size, study sites, methods, total budget, and a picture or other graphic describing the study. An example of a CDMRP-compliant quad chart can be found at: https://cdmrp.org/Program_Announcements_and_Forms/
Supporting Documentation	Start each document on a new page with complete header information. Include only those components described below; inclusion of items not requested may result in the removal of those items or administrative withdrawal of the application.
	References Cited: List the references cited in the Research Methods (including URLs if available) using a standard reference format that includes the full citation (i.e., author[s], year published, title of reference, source of reference, volume, chapter, page numbers, and publisher, as appropriate).

Item	Description
	List of Abbreviations, Acronyms, and Symbols: Provide a list of all abbreviations, acronyms, and symbols used in the application.
	Facilities, Existing Equipment, and Other Resources: Describe the facilities and equipment available for performance of the proposed project and any additional facilities or equipment proposed for acquisition at no cost to the award. Indicate whether Government-furnished facilities or equipment are proposed for use. If so, reference should be made to the original or present Government award under which the facilities or equipment items are now accountable.
	Publications or Patent Abstracts *(three-document limit)*: Include relevant publication URLs or patent abstracts. If publications are not publicly available, then a copy/copies of the published manuscript(s) must be included here. Extra items will not be reviewed.
	Letters of Organizational Support *(two-page limit per letter)***:** Provide a letter (or letters, if applicable), signed by the Department Chair or appropriate organization official, reflecting the institution's commitment to the completion of the trial, including laboratory space, equipment, and other resources available for the project.
	Letters of Collaboration (if applicable) *(two-page limit per letter)***:** Provide a signed letter from each collaborating individual or organization that will demonstrate that the PI has the support or resources necessary for the proposed work. Letters of support from a collaborating pharmaceutical company are welcomed and desired.
	Research & Related Senior/Key Person Profile: All applications must include: o PI Biographical Sketch (*four-page limit*) o PI Previous/Current/Pending Support (*no page limit*) o Key Personnel Biographical Sketches (*four-page limit each*) o Key Personnel Previous/Current/Pending Support (*no page limit*) Forms available on the website: https://pasa.rti.org/About/Grant-Program

B.3 Full Application Format

All applications should be submitted as a single PDF file, except for the full budget PDF form, which should be a separate file. All text should be in Calibri with a font size of no less than 11. All margins should be at least one inch. Inclusion of URLs to provide additional information is prohibited in all sections.

IV. Full Application Review and Selection Process

A. Peer Review

To determine technical merit, all applications will be evaluated by a peer-review committee according to the following scored criteria, which are of equal importance. For multisite studies, feasibility, personnel, and environment will be evaluated across all sites.

Research Rational, Strategy, and Feasibility

- How well the scientific rationale supports research on the proposed compound(s) for treatment of ASUD comorbid with PTSD or TBI. The feasibility of such research, as demonstrated by a critical review and analysis of the literature, supporting data, and logical reasoning.
- How well the application describes existing preclinical and clinical trial research of the proposed compound(s) and justifies additional study for treatment of ASUD comorbid with PTSD or TBI.
- How well the application acknowledges potential problems or delays and addresses alternative approaches and solutions.

- **Impact**
  - How the proposed research, if successful, will:
    - Promote greater understanding of the treatment of ASUD comorbid with PTSD or TBI
    - Promote the development of improvements in pharmacotherapies for ASUD comorbid with PTSD or TBI
    - Support potential approval and marketing of pharmacotherapies for ASUD comorbid with PTSD or TBI
- **Personnel**
  - How the background and expertise of the PI(s) and other key personnel demonstrate their abilities to perform the proposed work.
  - How the levels of effort by the PI(s) and other co-investigators are appropriate to ensure the successful conduct of the project.
  - How the PI(s)'s and co-investigators' record(s) of accomplishment demonstrate their abilities to accomplish the proposed work.
- **Environment**
  - How the scientific environment is appropriate for the proposed research.
  - How the research requirements are supported by the availability of and accessibility to facilities and resources.
  - How the quality and extent of organizational support are appropriate for the proposed research.
- **Transition Plan**
  - Whether collaborations with industry or other institutions exist that will be used to provide continuity of development to inform study design, sample size, and dosing for future clinical trials.

In addition, the following unscored criteria will also contribute to the overall evaluation of the application:

- **Budget**
  - Whether the budget is appropriate for the proposed research and within the funding limitations.
- **Application Presentation**

- To what extent the writing, clarity, and presentation of the application components influence the ease of review and the understanding of the reviewers.

B. Programmatic Review

Following the Peer Review, the Programmatic Review of applications will be made by the PASA Management Core and the GSC. The GSC will make funding recommendations using the following criteria:

- Ratings and evaluations of the peer reviewers
- Relevance to the mission of the PASA, as evidenced by the following:
  - Relative impact
  - Program portfolio composition
  - Programmatic relevance
  - Adherence to the intent of the award mechanism

Final selection of research grants will be made by the GSC.

V. Award Negotiation

If your application is recommended for funding by the GSC, award negotiations will be held between your institution and the PASA Management Core to establish the scope of the final award consistent with the recommendations of the GSC and subject to final approval of the GSC. All official negotiations of the budget, terms, and conditions of any resulting award will be conducted between the Business Official of your institution and the RTI Subcontracts Specialist. All subawards, and changes to all subawards that result in substantive changes to the budget, including major modifications of subawards and changes across cost categories, require approval from the United States Army Medical Research Acquisition Agency.

VI. Post-Award Requirements

A. Protocol

Within 4 months of study award, all studies shall develop a protocol in conjunction with the Management Core and submit for review and approval by the PASA Leadership and obtain Institutional Animal Care and Use Committee (IACUC) and Animal Care and Use Review Office (ACURO) approval. The protocol must follow the PASA Protocol Template on the PASA website (https://pasa.rti.org/About/Grant-Program). The protocol must be approved by PASA Leadership in writing prior to the initiation of study activities with animal subjects. ACURO approval is required prior to any spending of DoD funds provided through the PASA Consortium on animal purchasing or experimentation.

B. Study Manual of Procedures

In addition to the study protocol, a study manual of procedures (MOP) will be developed by the study team in conjunction with the Management Core and submitted to the PASA Leadership for review and approval. The MOP must be approved in writing by the PASA Leadership prior to the initiation of study activities with animal subjects.

Most preclinical studies funded by the PASA Consortium must be conducted in accordance with Good Laboratory Practice (GLP) requirements. Some basic science studies may not require adherence to

GLP and a determination will be made concerning GLP in consultation between the PI and the PASA Management Core. The links below provide information concerning these requirements.

GLP:

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=58

C. Reporting

Quarterly and annual progress reports will be required in the format shown on the PASA website (https://pasa.rti.org/About/Grant-Program). In addition to written progress reports, oral presentations may be requested, particularly to the GSC.

D. Quality Assurance

During MOP development, a quality assurance plan must be developed in line with PASA's quality assurance guidelines. This plan will include details of records maintenance at the site, timely data recording, verification, and routine reporting/submission of data to the PASA Management Core and planned checks data consistency.

Appendix A: Proposal Cover Sheet

Project Title:

Principal Investigator's Name:
Position/Title:
Department:
Organization Name:
Street:
City:
State:
Zip:
E-mail:
Phone:

Direct costs:
Indirects:
Total costs:

Proposed Start Date:

Proposed End Date:

PASA target disorders: (please list all that apply)

- Alcohol
- Opiates
- Marijuana
- Stimulants
- Other substance (specify)
- PTSD
- TBI