

Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium
PASA Study Research Planning Program (SRPP)
Compound Development Planning Grant Application
Request for Application (RFA) #4a: [FY19-Round 1]
Release: March 18, 2019

SUBMISSION AND REVIEW DATES

- Letter of Intent Deadline 22-Apr-19
- Full Application Deadline 03-Jun-19
- Peer Review Process & Programmatic Review 22-Jul-19
- Notification of Award Recommendation 05-Aug-19
- Award Negotiations 19-Aug-19

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

Small-cost and short-duration planning grant awarded to investigators concerning a specific compound or combination of compounds. Designed to determine the clinical development plan and associated studies needed to advance the compound to FDA approval for ASUD treatment. The protocol for the first study will be developed as part of the planning grant and will be considered for funding and implementation by the PASA Consortium.

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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 TBI as these comorbidities are common in a military population. Alcohol use disorder (AUD) is the most common ASUD in the military, but opiate use disorder also has developed significant clinical importance because of prolonged pain treatments with opiates. 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 PASA SRPP is requesting applications for planning grant(s) to support early phase, proof of concept clinical trials to develop/evaluate a compound(s) for treatment of any ASUD comorbid with PTSD or TBI to be conducted as part of the Consortium in collaboration with the applying investigators. The planning grants will provide support for the extensive efforts required to determine the clinical development plan needed to advance the compound to FDA approval for ASUD treatment through development of a series of studies, some of which might receive funding through the Consortium. A productive planning grant will yield a clinical development plan, a protocol for the first study in the plan, and FDA approval or exemption for the plan and protocol. The first study will be considered for funding and implementation by the PASA Consortium. Preference will be given to compounds that have potential value to a pharmaceutical company to gain support for final development by the company. The expected duration of the planning grant is 9-12 months.

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. Clinical trials that include military Service member (SM) and Veteran populations are highly desirable because these comorbidities are common in these populations.

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 human clinical trials supported by the Consortium. 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. The Management Core will coordinate the regulatory strategy for FDA compliance, in collaboration with the industry or academic sponsor and collaborators, leading to potential product development and licensing. Additional information about PASA is available on its website: <https://pasa.rti.org/>.

D. Expert Advisers

In addition to the Management Core, the National Institute of Alcohol Abuse and Alcoholism (NIAAA) is available to provide consultation, guidance and expertise on the design, conduct and analysis of relevant clinical studies evaluating potential medications for treatment of PTSD-Alcohol Use Disorders. In addition, depending on the relevance of the proposed studies to the current medication development goals of NIAAA, and on the availability of funds, NIAAA will consider contributing support to responsive, meritorious application(s) if the study is ultimately approved to move forward. For example, NIAAA might consider expanding the populations being studied beyond SMs and Veterans by funding additional civilian sites. Applicants interested in consideration of NIAAA cofunding are encouraged to contact Dr. Raye Litten at NIAAA (rlitten@mail.nih.gov).

E. Study Sites with Military and Veteran Focus

Applications should address topics with a focus on military SMs and Veterans. Those applications that do not demonstrate a military or Veteran focus are less likely to receive a positive review. To this end, the Management Core is available to facilitate collaboration between applicants and military and Veteran medical centers. The Consortium also has contacts at many VA medical centers and military treatment facilities (MTFs) that can be used to establish collaborators and clinical sites to support clinical studies. Additional information concerning such collaborations can be obtained by contacting PASA_RFA@rti.org.

F. Pharmaceutical Company Participation

Obtaining FDA approval for a pharmacotherapy usually is facilitated by partnership with a pharmaceutical company for Phase 3 testing and eventual New Drug Application. Although developing such a commercial partnership may not be possible for the studies to be funded by the PASA SRPP, it is strongly recommended that such a commercial partner be obtained as early in the medication development process as possible. A demonstrated relationship with a pharmaceutical company with a path to eventual marketing of the pharmacotherapy will be a factor in the award selections.

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 only soliciting for planning grants under Aim 3: Proof of concept human trials. A separate RFA is available for basic science research studies (Aim 2).

The planning grants considered under this RFA are for promising compound(s) for which a development plan is needed to layout the Phase I or Phase II studies that will be required before pivotal Phase III studies can be conducted. Examples of studies of potential compounds should involve small numbers of subjects and include assessment of medical safety and of potential doses for efficacy in humans with ASUD comorbid with PTSD or TBI. The studies can range from Phase I through late Phase II including, for example,

- drug/substance safety interaction studies and PK studies, especially when the compound has not previously been co-administered with the substance of abuse (such as alcohol),
- dose finding studies, and
- single site or multisite safety and preliminary efficacy trials intended to show sufficient evidence of efficacy for a future Phase III clinical trial.

If you have questions about whether you should apply for a planning grant, please send a note describing your situation to PASA_RFA@rti.org.

B. Planning Grant for Developing Promising Compounds

Small-cost and short-duration planning grants may be awarded to an investigator concerning a specific compound or combination of compounds. These grants are designed to determine the clinical development plan (CDP) needed to advance the compound to FDA approval for ASUD treatment comorbid with PTSD or TBI through a series of studies, some of which might be funded through the PASA Consortium. Preference will be given to compounds that have potential value to a pharmaceutical company to gain support for final development by the company. Participation in the grant by a company will be highly valued.

III. Submission Information

A. Types of Studies to be Awarded

Type	Period of Performance	Maximum Total Cost (Direct and Indirect)
Planning Grant	9-12 months	\$150,000

Note: *Maximum total cost includes direct plus indirect costs.*

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. Answers will be provided on a rolling basis, and just after May 6, 2019, the PASA Administrator will distribute a list of all the questions received along with the answers provided.

All final applications must be submitted as a PDF file by e-mail no later than **June 3, 2019**, to:
PASA SRPP Administrator
PASA_RFA@rti.org

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; and
- A brief overview of the proposed compound including the existing research completed to date with a specific focus on the researcher’s experience with the compound.

The LOIs are largely 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 listed PI(s) to share that information.

B.2 Compound Planning Grant Application Submission Requirements

The application consists of the following components:

Item	Description
Proposal Cover Sheet	See Appendix A for this template.
Title	Provide the title of the proposed planning grant.
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. For the purposes of the planning grant, please focus only on the primary site/investigator being proposed (if that site is an academic institute that traditionally pairs with a VA or MTF to conduct any study, please include details of the associated VA or MTF). No detailed information on other secondary proposed sites is required.
Compound Rationale/Research Gap/Impact (1-page limit)	Please describe rationale, research gap, and impact of the proposed compound or compounds. The proposed compound should address an area of need targeted by the Consortium. All compounds 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 compounds will align with DoD research and clinical goals to maximally benefit SMs and Veterans.
Justification (2-page limit)	Justification for human research. Provide a summary of research completed by the PI(s) or other investigators to justify the ability to conduct any IND studies of this compound in this field. Determine, to the best of existing knowledge, the current location of the proposed compound(s) within the regulatory pathway (e.g., past use in substance

Item	Description
	using populations, PK studies in presence of substance use, substance use interaction studies, single site studies assessing efficacy and safety for substance use disorder).
Future Clinical Trial Needs (2 pages)	Describe, to the best of your knowledge, the current trial needs for this compound. This should include but not be limited to the following: <ul style="list-style-type: none"> • Describe the potential need for an interaction study of the proposed compound and the substance for treatment targeted (i.e., a study where healthy individuals are exposed jointly to compound and ethanol challenge for AUD targeted compounds). • Describe the potential need for a PK study to assess the effect of substance use on the pharmacokinetics of the compound. • Describe the need for a dose-finding study of the proposed compound. • Describe the potential need for a small, single-site outpatient study assessing the preliminary efficacy and safety of the compound.
Innovation (1-page limit)	State how the study of the compound 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 project to the research community and how it will not replicate current studies, but moves beyond with an innovative approach or objectives.
Research Performance Sites (1-page limit)	A description of the proposed research site. Focus only on the primary site/investigator being proposed (if that site is an academic institute that traditionally pairs with a VA or MTF to conduct any study, please include details of the associated VA or MTF). No detailed information on other secondary sites is required.
Pharmaceutical Company Collaboration/Regulatory Pathway Progression Potential (1-page limit)	Address the proposed collaboration and process that would be used to continue to move this compound through the regulatory pathway toward a new label/indication if the PASA-funded studies provided evidence supporting continued investigation.
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 (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).
	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 primary site/investigator being proposed (if that site is an academic institute that traditionally pairs with a VA to conduct any study, please

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Item	Description
	include details of the associated VA). No detailed information on other secondary sites is required.
	Publications or Patent Abstracts (<i>three-document limit</i>): 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 (<i>two-page limit per letter</i>): 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. Please focus only on the primary site/investigator being proposed (if that site is an academic institute that traditionally pairs with a VA to conduct any study, please include details of the associated VA). No detailed information on other secondary sites is required.
	Letters of Collaboration (if applicable) (<i>two-page limit per letter</i>): 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.
	Letters Confirming Access to Military or VA Patient Populations or Resources (if applicable) : If the proposed research plan involves access to active duty military or VA patient populations or resources, a letter of support, signed by the lowest ranking person with approval authority, confirming such access is desired but not required as part of the planning grant application. If access cannot be confirmed at the time of the planning grant application submission, it will need to be obtained during the planning grant funding period.
	Research & Related Senior/Key Person Profile: All applications must include: <ul style="list-style-type: none"> o PI Biographical Sketch (<i>four-page limit</i>) o PI Current/Pending Support (<i>no page limit</i>) o Key Personnel Biographical Sketches (<i>four-page limit each</i>) o Key Personnel Current/Pending Support (<i>no page limit</i>) Forms available on the website: https://pasa.rti.org/About/Grant-Program No detailed information on other secondary sites is required.

B.2 Full Application Format

All full applications should be submitted as a single PDF file. All text should be in Calibri with a font size of no less than 11. All margins should be at least one inch.

IV. Full Application Review and Selection Process

A. Peer Review

To determine technical merit, all applications will be evaluated according to the following scored criteria, which are of equal importance.

Research Rational, Strategy and Feasibility

- How well the scientific rationale supports clinical trial research on the proposed compound 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 early phase clinical trials for treatment of ASUD comorbid with PTSD or TBI.
- How well the application acknowledges potential problems or delays and addresses alternative approaches and solutions.
- If applicable, how well the application provides evidence of availability of and access to the necessary study populations or resources.
- If applicable, how well the PI addresses the availability of and access to SMs or Veterans for any subsequently funded clinical trials and the prospect of their participation.
- How well the application assesses the likely next steps needed for continuing the compound along the regulatory pathway.
- Whether the investigators demonstrate an ability via pharmaceutical collaboration or otherwise for compound to continue to progress long term on regulatory pathway.
- **Impact**
 - How the proposed research planning grant, 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 contribute to the overall evaluation of the application:

- **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 Leadership Group. To make funding recommendations, the following criteria are used by programmatic reviewers:

- 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 planning grants will be made by the GSC.

V. Award Negotiation

If your application is recommended for planning grant funding, award negotiations will be held between your institution and the PASA Management Core to establish the scope of the planning grant 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. Activities

Within 9-12 months of planning grant award the following activities will be completed by the investigators in collaboration with the PASA Consortium:

1. Compilation of existing supporting basic science and clinical trial work done to date on

compound

2. Meetings with potential pharmaceutical collaborators to identify interest and potential role
3. Creation of CDP, draft of first study synopsis and pre-IND meeting packet
4. FDA pre-IND meeting
5. Incorporation of FDA comments into CDP and development of study protocol
6. Identification of unique case report forms
7. FDA submission of first protocol (or exemption)
8. Development of draft case report forms
9. Address any clinical hold issues (if applicable) and finalized study protocol
10. Identify sites and develop budget
11. Peer Review of first study protocol by Data and Safety Monitoring Board
12. Submit CDP and first study protocol to GSC for funding consideration.

B. Deliverables

Within 9-12 months of planning grant award four deliverables are expected:

1. A CDP for the compound that identifies firmly what next study(ies) are required for moving the compound along the regulatory pathway.
2. A protocol and associated budget for the immediate next step study. The content of the protocol shall follow the template provided on the PASA website <https://pasa.rti.org/About/Grant-Program>.
3. FDA input on the CDP and approval or exemption for first protocol.
4. Final submission packet to PASA Leadership and GSC to request approval and funding for first study. Materials to include study protocol, budget, and CDP.

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. Other Expectations of Clinical Research Studies

If a clinical study from your clinical development plan is selected for funding and implementation, then you will be expected to:

- Designate a lead site PI and develop a succession plan upon request in case of departure of the site PI; the site PI must agree to adhere to the Consortium SOP.
- Collaborate with other Consortium basic research and clinical trial sites.
- In accordance with Consortium-developed guidelines, maintain a minimum combined participant accrual across all Consortium-associated clinical studies.
- As applicable, provide a Clinical Research Coordinator who will interact with the Clinical Research Coordinators of other basic research and clinical trial sites and the Consortium Clinical Research Manager at the Management Core to expedite and guide clinical protocols through regulatory approval processes and to coordinate patient accrual and study activities across sites.

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- Implement the Consortium's core data collection methodology and strategies.
- Comply with Consortium-developed quality assurance and quality control procedures, as appropriate, including:
 - Participation in an on-site monitoring program to be managed by the Management Core.
 - Implementation of the Consortium-developed management plan for acquisition and aggregation of protocol-specified specimens, biological fluids, and relevant data to the appropriate laboratories for testing or storage.
 - Submission of appropriate data and materials to allow for verification and review of protocol-related procedures (e.g., pathology, imaging techniques, surgical methods, and therapeutic use).
- Implement procedures established by the Management Core for ensuring compliance with FDA requirements, as appropriate.
- Implement procedures established by the Management Core to meet local Institutional Review Board and United States Army Medical Research and Materiel Command (USAMRMC) Human Research Protections Office requirements for the conduct of clinical trials and the protection of human subjects.
- Participate in Consortium-developed procedures for the timely publication of major findings.
- Participate in Consortium-developed procedures for resolving intellectual and material property issues among organizations participating in the Consortium.
- Participate in the preparation of written and oral briefings to the GSC and USAMRMC staff at 1-day meetings to be held in the Baltimore, MD/Washington, DC, area.
- Assist with the preparation of quarterly written progress reports, annual reports, and a final comprehensive report.
- Prepare for and participate in site visits.

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