Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium

PASA Study Research Planning Program (SRPP)
Compound Development Planning Grant Application
Request for Application (RFA) #3a: [FY18-Round 1]

Release: June 27th, 2018

SUBMISSION AND REVIEW DATES AND TIMES

- Full Application Deadline 22-Aug-18
- Peer Review Process & Programmatic Review 24-Oct-18
- Notification of Award Recommendation 31-Oct-18
- Award Negotiations 14-Nov-18

Request for Application (RFA) #3a: [FY18-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 (CDP) needed to advance the compound to FDA approval for ASUD treatment through a series of studies, some of which might be funded through 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 posttraumatic stress disorder (PTSD), because this comorbidity is common in a military population along with mild to moderate traumatic brain injury (TBI). Alcohol use disorder (AUD) is the most common ASUD in the military, but opiate use disorder (OUD) also has developed significant clinical importance due to prolonged pain treatments with opiates. Since 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. While 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 PASA SRPP is requesting applications for planning grant(s) to support early phase, proof of concept clinical trials to develop/evaluate a compound(s) to be conducted as part of the Consortium in collaboration with the applying investigators. The planning grants will determine the clinical development plan needed to advance the compound to FDA approval for ASUD treatment through 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 for the plan and first study. 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 6 months.

B. Program Description

The PASA Consortium is administered by a Management Core led by RTI International (RTI) in collaboration with the Baylor College of Medicine (BCM). The PASA Consortium Leadership team consists of the Principal Investigator Rick Williams, PhD, from RTI and the 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. Clinical

trials that include military Service member (SM) and Veteran populations are highly desirable because this comorbidity, along with mild to moderate TBI, is 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 Government Steering Committee formed by the U.S. Department of Defense. The Management Core will provide oversight and coordination for future proof-of-principle basic research studies and 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 sponsor, 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 following are available for consultation:

1. National Institute of Alcohol Abuse and Alcoholism (NIAAA)
2. US Department of Veterans Affairs (VA)

NIAAA and VA are 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 the NIAAA and VA, and on the availability of funds, the NIAAA and VA will consider contributing support to responsive, meritorious application(s) if the study is ultimately approved to move forward. For example, the NIAAA might consider expanding the populations being studied beyond Service Members and Veterans by funding additional civilian sites. Similarly, the VA might consider expanding the number of VA sites by funding those sites to provide more subjects for comparisons involving behavioral interventions such as progressive exposure therapy or active medications such as to paroxetine. Applicants interested in consideration of NIAAA co-funding are encouraged to contact Dr. Raye Litten at NIAAA (rlitten@mail.nih.gov) and consideration of VA co-funding are encouraged to contact Dr. Katrina Foster at the VA (Katrina.Foster@va.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 and/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 (VAMCs) 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 (NDA). While 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. PASA Leadership has recruited several interested commercial partners with potential compounds to test. A discussion of these potential compounds for use can be arranged by contacting PASA_RFA@rti.org. 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. To 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 will be released for basic science research studies (Aim 2), and for ready-to-implement human proof-of-concept trials (Aim 3) which have an established protocol and FDA approval for the study.

The planning grants considered under this RFA are for promising compound(s) for which a development plan is needed to layout the Phase I and 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 in ASUD humans and of potential doses for efficacy in humans with ASUD, PTSD and possibly 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,
- 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 not 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 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
Planning Grant	6 months	$30,000

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 August 8, 2018. Answers will be provided on a rolling basis, and just after August 1, 2018, 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 **August 22, 2018** to:
PASA SRPP Administrator
PASA_RFA@rti.org

B.1 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, and/or VA personnel. Include an organizational chart and briefly describe the roles and responsibilities of the study personnel.

Item	Description
	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 to conduct any study, please include details of the associated VA). No detailed information on other secondary proposed sites is required.
Compound Rationale/Research Gap/Impact (1 page limit)	Please describe rational, research gap and impact of the proposed compound or compounds. The proposed compound should address a targeted Consortium area of need. All compounds must be in line with PASA objectives and Aims. These Aims and priorities may change based upon feedback from the Government Steering Committee. 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 done to date by yourself or other investigators to justify the ability to conduct any IND studies of this compound in this field and to determine to the best of existing knowledge, where within the regulatory pathway the compound may currently be (e.g. past use in substance 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: o 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). o Describe the potential need for a PK study to assess the effect of substance use on the pharmacokinetics of the compound o Describe the need for a dose-finding study of the proposed compound. o 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 and/or VA healthcare 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 and/or objectives.

Item	Description
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 to conduct any study, please include details of the associated VA). 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 towards 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 include details of the associated VA). No detailed information on other secondary sites is required.
	Publications and/or Patent Abstracts *(three-document limit)*: Include relevant publication URLs and/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. 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) (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.
	Letters Confirming Access to Military or VA Patient Populations or Resources (if applicable): If the proposed research plan involves access to active duty military and/or VA patient populations or resources,

Item	Description
	include a letter of support, signed by the lowest ranking person with approval authority, confirming such access. If access cannot be confirmed at the time of application submission, the Government reserves the right to withhold or revoke funding until the PI has demonstrated support for and access to the relevant population(s) and/or resources.
	Research & Related Senior/Key Person Profile: All applications must include: **o** PI Biographical Sketch (*four-page limit*) o PI Current/Pending Support (*no page limit*) o Key Personnel Biographical Sketches (*four-page limit each*) o Key Personnel Current/Pending Support (*no page limit*) 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 and/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 pre-clinical and clinical trial research of the proposed compound and justifies additional early phase clinical trials for treatment of ASUD comorbid with PTSD and/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 and/or resources.

- If applicable, how well the PI addresses the availability of and access to SMs and/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, PTSD and/or TBI
    - Promote the development of improvements in pharmacotherapies for ASUD, PTSD and/or TBI
    - Support potential approval and marketing of pharmacotherapies for ASUD. PTSD and/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 and/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:

- **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 section of planning grants will be made by the Government Steering Committee.

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 (USAMRAA).

VI. Post Award Requirements

A. Protocol

Within 6 months of planning grant award two deliverables are expected:

1. A development plan 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 to be submitted for review and approval by the PASA Leadership and the PASA GSC. The content of the protocol shall be similar to the example provided on the PASA website https://pasa.rti.org/About/Grant-Program.

B. 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.

C. 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.
- 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 and/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 (IRB) and United States Army Medical Research and Materiel Command (USAMRMC) Human Research Protections Office (HRPO) 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 one-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:
Email:
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