Pharmacotherapies for Alcohol and Substance Use Disorder Alliance (PASA)
Study Research Planning Program (SRPP)
Compound Development Research Pre-Clinical Award Application
Request for Application (RFA) #7b: [FY23; Round 1]

Release: June 2, 2023

SUBMISSION AND REVIEW DATES

• Letter of Intent Due	6/30/2023
• Full Application Due	7/28/2023
• Peer Review Process Ends	8/14/2023
• Programmatic Panel Review	Late September 2023
• Notification of Award Recommendations	Early October 2023
• Award Negotiations Begin	Mid October 2023

Request for Application (RFA) #7b: [FY23; Round 1]
Synopsis

Full study implementation awards for proof-of-principle pre-clinical animal research to determine which compounds are most appropriate for human research trials. Separate RFAs are available for basic science non-clinical research studies (e.g., in-silico research) and planning awards for human participant clinical trials.

Additional details and associated templates for this RFA are available at: https://pasa-research.org/funding-opportunities

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I. Funding Opportunity Description

A. Introduction and Intent of Award Mechanism

The **P**harmacotherapies for **A**lcohol and **S**ubstance Use Disorder **A**lliance (PASA) is funded by the Congressionally Directed Medical Research Programs (CDMRP) (https://cdmrphealth.mil/) as part of its Alcohol and Substance Use Disorders Research Program (ASUDRP) consortium awards (W81XWH-17-ASADRP-CA and W81XWH-21-ASADRP-CA). The PASA's goal is to fund study applications that explore integrated approaches to address ASUD especially comorbid ASUD with PTSD and other psychological disorders and reduce the number of opioid and other substance use-related deaths through multidisciplinary, team-based research efforts that translate basic knowledge into enhanced clinical pharmacological treatment protocols and enhanced quality of life for service members, Veterans, and the American public. These medications will ideally address the comorbidity between ASUD and PTSD or other psychological disorders because these comorbidities are common in the military and veteran populations. Alcohol use disorder (AUD) is the most common ASUD in these populations, but opiate use disorder (OUD) 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 pre-clinical, basic animal research to determine compounds to be used for treatment of any ASUD (meaning AUD, SUD or combined ASUD) comorbid with PTSD or other psychological disorders most appropriate for future human research trials leading to enhanced quality of life for service members, Veterans, and the American public. Separate RFAs are available for basic science non-clinical research studies (e.g., in-silico research) and planning awards for human participant clinical trials.

B. Program Description

The PASA is administered by a PASA Core led by RTI International in collaboration with the Baylor College of Medicine (BCM). The PASA Leadership team consists of Principal Investigator Tracy Nolen, DrPH from RTI and co-Principal Investigators Tom Kosten, MD, from BCM and Nathan Vandergrift, PhD, from RTI. Oversight of PASA is provided by a Programmatic Panel assembled by the CDMRP.

The goal of the PASA 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 other psychological disorders. These medications will ideally address the comorbidity between ASUD and other psychological disorders.

C. The PASA Core

The PASA Core is responsible for soliciting and prioritizing applications. Successful applications will be recommended for funding by the Programmatic Panel assembled by the CDMRP. The PASA Core will provide oversight and coordination for future proof-of-principle basic research studies, receive all study data in a timely manner and function as a data repository, and provide analytic support in designing study randomization and performing statistical analyses.

The PASA 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 PASA Core. The PASA Core

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

II. Research Focus

A. Research Aims

The PASA has three broad aims:

1. Discover: Test new chemical entities and repurpose existing medications in strictly pre-clinical and non-clinical models of ASUD with comorbid PTSD and other psychological disorders.
2. Phase 1 First-in-Human Safety: Conduct clinical trials of potential medications that include assessment of medical safety and doses for potential efficacy in subjects with ASUD and comorbid PTSD and other psychological disorders.
3. Phase 2 Efficacy: Conduct multiple site clinical trials to test preliminary efficacy and safety of potential medications or medication combinations in humans with ASUD and comorbid PTSD and other psychological disorders, and to also explore precision medicine tools for matching patients to these medications.

B. Research Areas of Emphasis

1. Improved formulations to treat ASUD with comorbid substance use
2. Improved formulations to treat ASUD with comorbid PTSD and other psychological disorders
3. Stronger, longer-duration formulations to counteract opioid (including fentanyl analogs) overdose
4. New formulations and/or combinations of existing medications to improve treatment compliance, prevent relapse, and reduce risk of misuse
5. Novel medications and immunotherapies to treat substance and/or ASUD
6. New medication targets for the treatment of substance and/or ASUD

For this RFA, we are soliciting for research awards under Aim 1 pre-clinical animal research studies. The research award must address at least one research area of emphasis. Separate RFAs are available for basic science non-clinical research studies (Aim 1; e.g., in-silico research) and planning awards for human participant clinical trials (Aims 2 and 3).

C. Pre-clinical Basic Research

Discovery of new medications for ASUD comorbid with PTSD or other psychological disorders 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 other psychological disorders 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 other psychological disorders models and the effect on the ASUD models after an animal has developed the aberrant behaviors of the PTSD or other psychological disorder models.

III. Submission Information

A. Types of Studies to be Awarded

Type	Period of Performance	Maximum Total Cost (Direct and Indirect)
Pre-clinical Basic Research	18 months	$600,000

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; with answers provided on a rolling basis and posted on a FAQ page of the PASA website.

B.1 Letter of Intent

A letter of intent (LOI) must be submitted prior to submission of the full application. 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.

All LOIs must be submitted as a PDF file by e-mail no later than 11:59 PM Eastern Time on **June 30, 2023;** to:
PASA_RFA@rti.org

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

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 28, 2023;** to:
PASA_RFA@rti.org

The full application consists of the following components:

Item	Description
Application Cover Sheet	See Appendix A for this template.
Title	Provide the title of the proposed pre-clinical project.
Abstract	Include an abstract of the proposed pre-clinical research.
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.
Research Rationale (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 PASA and be in line with PASA objectives and aims. These aims and priorities may change based on feedback from the Programmatic Panel. The rationale should also clearly describe how the proposed study will align with DoD research and clinical goals to maximally benefit service members (SMs) and Veterans. Describe the scientific rationale, and research strategy of the proposed study for the treatment of ASUD comorbid with PTSD or other psychological disorders. The proposed study should address an area of emphasis targeted by the PASA. Describe the feasibility of the research to include a critical review and analysis of the literature and supporting data.
Research Strategy and Feasibility (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. Rigor of Experimental Design: All projects should adhere to accepted standards for rigorous study design and reporting to maximize the reproducibility and translational potential of preclinical research. Applicants should consult the Animal Research: Reporting In Vivo Experiments (ARRIVE) guidelines 2.0 (ARRIVE) guidelines to ensure relevant aspects of rigorous animal research are adequately planned for and, ultimately, reported. The ARRIVE 2.0 guidelines can be found at: https://arriveguidelines.org/arrive-guidelines
Impact and Innovation (1-page limit)	State how the project has the potential to significantly inform military or VA health care and practice and promote a greater understanding of the treatment of ASUD comorbid with PTSD or other psychological

Item	Description
	conditions and reduce the number of opioid and other substance related deaths. A successful application will also describe how the proposed research: • Meaningfully expands on existing research without overlapping existing research/current studies • Uniquely contributes to the understanding of ASUD comorbid with PTSD or other psychological conditions and not replicate current studies but move beyond with an innovative approach or objectives. • Promotes the development of improvements in pharmacotherapies for ASUD comorbid with PTSD or other psychological conditions leading to approval and marketing.
Environment (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 to include the availability and accessibility to facilities and resources.
PASA Core Collaboration (1-page limit)	The PASA Core should be meaningfully integrated into the research to: • Support oversight and coordination of the project • Receive all study data in a timely manner and function as a data repository • 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 Core.
Laboratory Animal Protocol	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

Item	Description
	award, all study subaward funds will be subject to policies and restrictions based on the DoD source of this funding. • Budget to be submitted using R&R Budget form • Forms are available on the PASA website
Quad Chart	All applications must include a quad chart (separate from the application) 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://ebrap.org/eBRAP/public/Program.htm
Pharmaceutical Collaboration/ Regulatory Pathway Progression (1-page limit)	Address the proposed collaboration and process that would be used to provide continuity of development to inform study design, sample size and dosing to move this compound through the regulatory pathway in support of future clinical trials leading to a new label/indication if the study where to be successful.
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).
	• **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

Item	Description
	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 (4-*page limit*) o PI Previous/Current/Pending Support (*no page limit*) o Key Personnel Biographical Sketches (4-*page limit each*) o Key Personnel Previous/Current/Pending Support (*no page limit*) Forms available on the PASA website.

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.

- **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

- **Research Rationale, Strategy, and Feasibility**
  - How well the scientific rationale supports research on the proposed compound(s) for treatment of ASUD comorbid with PTSD or other psychological disorders.
  - How well the feasibility of such research is described by a critical review and analysis of the literature, supporting data, and logical reasoning.
  - How well the application defines the aims and objectives of the research and the necessary endpoints.
  - How well the application acknowledges potential problems or delays and addresses alternative approaches and solutions.

- **Impact and Innovation**
  - How the proposed research, if successful, will:
    - Promote greater understanding of the treatment of ASUD comorbid with PTSD or other psychological disorders and reduce the number of opioid and other substance use-related deaths.
    - Promote the development of improvements in pharmacotherapies for ASUD comorbid with PTSD or other psychological disorders.
    - Support potential approval and marketing of pharmacotherapies for ASUD comorbid with PTSD or other psychological disorders.
  - How the proposed research uniquely contributes to the understanding of ASUD comorbid with PTSD or other psychological conditions using an innovative approach or objectives.

- **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.

- **Laboratory Animal Protocol**
  - How well the animal protocol provides a justification for the animal used, the procedures or drugs used to minimize discomfort and a description of the search used to ensure that the experiment does not unnecessarily duplicate previous research.

- Pharmaceutical Collaboration/ Regulatory Pathway Progression 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.

- **Pharmaceutical Collaboration/ Regulatory Pathway Progression**
  - How well defined the proposed collaboration and process that would be used to provide continuity of development to inform study design, sample size and dosing to move this compound through the regulatory pathway in support of 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 PASA Core leaders will present the applications to the Programmatic Panel for their review. The Programmatic Panel will make funding recommendations using the following criteria:

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

Final recommendation of pre-clinical awards to be funded will be made by the Programmatic Panel.

V. Award Negotiation

If your application is recommended for funding by the Programmatic Panel, award negotiations will be held between your institution and the PASA Core to establish the scope of the final award consistent with the recommendations of the Programmatic Panel and subject to final approval of the Programmatic Panel. 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. Basic Milestones

The table below outlines basic milestone expectations for studies post award. Sites and the PASA Core shall communicate as deliverables are achieved and ensure progress aligns with the outline below. If additional time is needed due to unforeseen obstacles (i.e., COVID-19) this should be expressed immediately in orders to address accordingly.

Task	Responsible Party	Timeframe
Subcontract	Site and PASA Core	Within 4 months of study award
Protocol	Site and PASA Core	Within 4 months of study award
IACUC Submission	Site	Within 4 months of study award
ACURO Submission	PASA Core	Immediately following IACUC approval
MOP/Quality Assurance Plan	Site and PASA Core	Within 6 months of study award
Supplies Acquired	Site	Within 6 months of study award

B. Protocol

Within 4 months of study award, all studies shall develop a protocol in conjunction with the PASA 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

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 on animal purchasing or experimentation.

C. 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 PASA 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 pre-clinical studies funded by the PASA 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 Core.

D. Reporting

Quarterly and annual progress reports will be required in the format shown on the PASA website. In addition to written progress reports, oral presentations may be requested, particularly to the Programmatic Panel.

E. 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 Core and planned checks for data consistency.

F. Publications

A PASA priority is the rapid publication and presentation of study results in high quality peer reviewed journals and venues. Investigators should adhere to PASA publication policy which is available on the PASA website. A primary manuscript should be completed in a timely fashion. PASA Leadership will implement corrective action when 3 months have passed between final analysis and first draft, or 6 months have passed between final analysis and submission to a peer-reviewed journal; and an extension has not been requested or awarded.

Appendix A: Application 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
- Other psychological disorders (specify)