Pharmacotherapies for Alcohol and Substance Use Disorder Alliance (PASA)
Study Research Planning Program (SRPP)
Compound Development Research *Non-Clinical* Award Application
Request for Application (RFA) #7c: [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	8/28/2023
• Programmatic Panel Review	Late September 2023
• Notification of Award Recommendations	Early October 2023
• Award Negotiations Begin	Mid-October 2023

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

Full study implementation awards for proof-of-principle non-clinical research to determine which compounds are most appropriate for human research trials. Separate RFAs are available for pre-clinical, basic science animal research studies 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://cdmrp.health.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 non-clinical, basic science research (e.g., in-silico research) to determine compounds to be used for treatment of 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 pre-clinical animal research studies 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. PASA Core

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

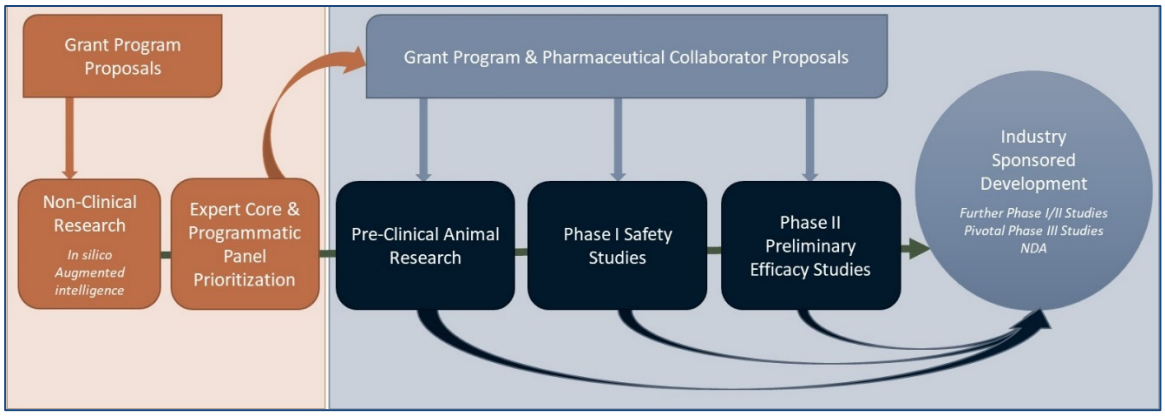
1. Improved formulations to treat ASUD with comorbid substance use
2. Improved formulations to treat ASUD with comorbid PTSD and other psychological disorders
3. Stronger, longer-duration formulations to counteract opioid (including fentanyl analogs) overdose
4. New formulations and/or combinations of 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 non-clinical research studies focused on ASUD comorbid with PTSD and other psychological disorders. The research award must address at least one research area of emphasis. Separate RFAs are available for basic science pre-clinical, animal research studies (Aim 1) and planning awards for human participant clinical trials (Aims 2 and 3).

C. Non-clinical Basic Research

The PASA has a well-established roadmap for pre-clinical animal studies and human participant clinical trials (Exhibit 1, blue box) that recently has been expanded to include earlier stage non-clinical research. Historically, potential compounds have been identified through pharmaceutical collaborators or interested investigators. Compounds with promising results may continue development within the PASA Consortium or through external industry-sponsored research.

Exhibit 1. PASA Translation Roadmap



The non-clinical research expansion is intended to increase the potential pool of compounds for investigation in subsequent pre-clinical studies and clinical trials. Approaches to identifying promising compounds for development or repurposing studies that leverage large-scale data through computational-based analysis include but are not limited to *in silico* and augmented intelligence research. Examples may be identifying genes that (a) influence underlying risk, (b) show altered expression, or (c) contain epigenetic changes associated with ASUDs, PTSD and/or other psychological disorders and subsequently compounds/therapeutics that interact with those genes. Empirical evidence supports these strategies, as drugs with such accompanying genetic evidence succeed in clinical trials twice as often as those without. Recent advances in genetics have led to the discovery of common changes in the human genome that influence psychiatric disorders including ASUDs and PTSD. In parallel, there is an increasing wealth of information from other biological domains including gene expression (protein coding, long noncoding, micro), and epigenetics including DNA methylation and histone modification. Integrated multi-omic investigations represent an opportunity to identify targets for translational studies not obvious via a single domain of investigation. However, discovery studies rarely focus on the specific goal of producing prioritized targets for future translational studies. The gap between discovery and translational efforts impedes progress toward clinical trials and identifying improved therapies for disorders disproportionally impacting SMs and Veterans.

The primary goal of the non-clinical approach is to bridge this gap within a systematic and rigorous framework to identify new biological targets for existing compound repurposing studies. This will be accomplished by (1) leveraging extant omic results and resources, (2) generating new supplemental data in discovery areas lacking sufficient depth, (3) creating an integrated catalog of results and biological targets, and (4) generating a prioritized list of existing candidate compounds for future repurposing studies. These resources will be shared with the drug repurposing community and PASA investigators to facilitate award program applications from a broader scope of compounds thereby leading to an increased success rate.

III. Submission Information

A. Types of Studies to be Awarded

Type	Period of Performance	Maximum Total Cost (Direct and Indirect)
Non-Clinical Basic Research	24 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 site(s) 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 Non-Clinical Award 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 non-clinical project.
Abstract	Include an abstract for the proposed non-clinical research project.
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.

Item	Description
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 (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 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 (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. The plans for obtaining and/or generating data should be clearly defined and feasible. Sample size estimates must be included and supported by a power analysis or other justification that demonstrates the adequacy of the sample size.
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 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 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/Research Sites	Applicants should describe how the project benefits from unique features of the scientific environment, or collaborative arrangements. A

Item	Description
(1-page limit)	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.
Dissemination/ Transition Plan (1-page limit)	Describe how the findings of this study will be disseminated to inform future pre-clinical studies and clinical trials
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.
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. • 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
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** *(3-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** *(2-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 study, including laboratory space, equipment, and other resources available for the project.
	• **Letters of Collaboration (if applicable)** *(2-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, a peer-review committee will evaluate all applications 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.

Study Rationale and Research Strategy

- How well the scientific rationale supports research for identifying potential compound(s) for treatment of AUD comorbid with PTSD or other psychological disorders.
- How well the feasibility of such research is demonstrated by a critical review and analysis of the literature, supporting data, and logical reasoning.
- How well the application describes existing non-clinical research intended to identify potential therapeutics for AUD comorbid with PTSD or other psychological disorders.
- 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 AUD 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 AUD comorbid with PTSD or other psychological disorders.
  - Support future potential approval and marketing of pharmacotherapies for AUD 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.

Environment/Research sites

- 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.

Dissemination/Transition Plan

- To what degree the plan describes how the findings will be disseminated to inform future pre-clinical studies and 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 non-clinical subcontracts 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	PI Site and PASA Core	Within 4 months of study award
Project Management Plan	PI Site and PASA Core	Within 4 months of study award
Any Required Regulatory Oversight Submissions Required	Site	Within 4 months of study award
Supplies Acquired	Site	Within 4 months of study award

B. Project Management Plan

Within 4 months of study award, all studies shall develop a project management plan in conjunction with the PASA Core and submit for review and approval by the PASA Leadership. The plan must detail all data sources and plans/timelines for obtaining the data, analyses to be completed to meet study aims, and measures that will be put in place to ensure quality The plan must be approved by PASA Leadership in writing prior to the initiation of study activities.

Non-clinical 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. The links below provide information concerning these requirements.

C. 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.

D. Quality Assurance

During Project Management Plan 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.

E. 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)