Pharmacotherapies for Alcohol and Substance Use Disorders (PASA) Consortium

Request for Full Applications

PASA Study Research Planning Program (SRPP) FY16

PASA SRPP FY16 Round 1

February 1, 2016

SUBMISSION AND REVIEW DATES AND TIMES

- **Application Submission Deadline: March 25, 2016 by 8:00 PM Eastern Time**
- **Peer Review: April 2016**
- **Programmatic Review: May 2016**
- **Notification of Award Recommendation: June 2016**
- **Award Negotiations: July-August 2016**

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I. Funding Opportunity Description

A. Invitation to Submit Full Application

Based on your submission of a pre-application for the Pharmacotherapies for Alcohol and Substance Use Disorders (PASA) Consortium (PASA) FY16 SRPP, we are requesting a full application per the details included in this RFA. Responses to this RFA will only be accepted if you received a letter of notification requesting submission of a full application.

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) and the Uniformed Services University of Health Sciences (USUHS). The PASA Consortium Leadership team consists of the PI Rick Williams, PhD, from RTI and the co-PI Tom Kosten, MD, from BCM. It is funded by the Congressionally Directed Medical Research Programs (CDMRP), as part of its Alcohol and Substance Abuse Research Program. CDMRP oversight is provided through a Government Steering Committee (GSC) impanelled by the CDMRP.

The goal of the PASA Consortium is to fund studies that aim to identify and develop new medications to improve treatment outcomes for alcohol and substance use disorders (ASUD), especially as related to traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD). 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 planning, prioritizing, and soliciting proposals, and providing oversight and coordination for future proof-of-principle basic research projects 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 and accelerate translation that would perhaps not otherwise be feasible without the Consortium approach. The Management Core contains multidisciplinary expertise and extensive experience in support of ASUD research. The Management Core will manage the regulatory strategy for FDA compliance leading to potential product development and licensing.

D. Study Sites with Military and Veteran Focus

Applications should address topics with a focus on military Service members (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. Information concerning such collaborations can be obtained by contacting PASA_RFA@rti.org.

E. Pharmaceutical Company Participation

Obtaining FDA approval for a pharmacotherapy usually is facilitated by partnership with a pharmaceutical company for the New Drug Application (NDA) filing and eventual phase III testing. While developing such a commercial partnership may not be possible for the studies to be funded by the PASA SRPP FY16, it is 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 factor in the award selections.

II. Research Focus

A. Research Aims

The PASA Consortium has three broad aims:

1. To DISCOVER novel medications and combination medications for ASUD.
2. To develop these medications through a rational PROOF OF CONCEPT pipeline model.
3. To conduct EFFICACY TRIALS of potential medication combinations in optimal target populations and explore functional genetic polymorphisms for matching patients to these medications.

The PASA Discovery aim will focus on testing new chemical entities and re-purposing existing medications in animal models of ASUD, PTSD and TBI disorders. New chemicals are encouraged, but plans need to consider that this Consortium cannot fund extensive toxicology testing in animals for filing Investigational Drug Applications (IND) to permit use in humans. Already FDA approved medications will typically be able to move directly into human studies, and this Consortium will fund human laboratory studies including surrogate measures of efficacy to examine interactions between these medications and either alcohol, opiates or other abused substances. Proof of concept human studies of potential medications 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. Efficacy trials involve larger numbers of patients and assess proof of concept in showing that these potential medications can reduce the target symptoms of ASUD and/or PTSD. For the current RFP, we will not be accepting efficacy trial proposals.

B. Discovery Aim

Discovery of new medications for ASUD and PTSD can greatly benefit from animal models of these disorders. Medications can reduce the aberrant behaviors in these models of PTSD and ASUD and potential dosages of these medications can be estimated for human studies. The ASUD models include alcohol or drug self-administration and conditioned place preference. The PTSD models include learned helplessness and predator attack. Other models are also possible and will be considered for both types of disorders. More importantly will be the interaction of substance intoxication and/or dependence with the PTSD models as well as the effect on the ASUD models after an animal has developed the aberrant behaviors of the PTSD models.

C. Proof of Concept Aim

Proof of concept studies involve medical safety assessments and some surrogate markers of clinical efficacy in ASUD and/or PTSD. Studies of ASUD may examine the effects of administering alcohol or some other abused drug while taking a new medication or combination of medications. Studies of PTSD may examine the ability of a new medication or combination of medications to reduce symptom expressions in human models of PTSD including virtual reality simulations, startle responses and other paradigms to elicit PTSD symptoms. These two types of studies would be most helpful if combined within a single overall study design. They are expected to last about 12-18 months to complete each study and to enroll about 30 to 50 subjects in either parallel groups or within-subjects cross-over studies

with the exact number to be justified by a sample size power analysis. Studies would be expected to last about 2 to 4 weeks per subject or, if a cross-over study, per evaluation period and examine either single agents or combinations of agents. Specific outcomes should include: a) medical safety in combination with alcohol (or the relevant drug of abuse), b) substance-induced subjective effects, c) craving reduction, d) reducing the selection of the substance in favor of monetary rewards, e) other surrogate markers of potential efficacy for ASUD and PTSD.

III. Submission Information

A. Types of Studies to be Awarded

Type	Period of Performance	Maximum Direct Cost
Discovery Aim Animal Studies	12 months	$100,000
Proof of Concept Aim Human Studies	18 months	$300,000

Note: Deviations from these from these time and funding limits will require written permission from PASA Leadership. Please see your letter of request for a full application for additional information.

B. Submission Requirements

All application components must be submitted by the applying PI. Because the invitation to submit an application is based on the contents of the pre-application, investigators cannot change the title or research objectives as part of the full application without written permission from the PASA Leadership or as specified as your letter of request for a full application. PIs and organizations identified in the pre-application should be the same as those intended for this full application submission.

A pre-submission teleconference will be held between the PASA Management Core staff and the study PI and his/her investigator team. The purpose of the teleconference is to review the feedback from the review of the pre-applications and to explain the support available from the Management Core in the conduct of each study. A plan for the activities to be conducted by the study team and the Management Core will be determined during the teleconference.

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.

The application consists of the following components:

- **Proposal Cover Sheet**. See Appendix 1 for this template.
- **Title**. Provide the title of the proposed project.
- **Study Personnel. (3-page limit)** Demonstrate that the PIs, collaborators, and other researchers are well suited to the project and have an ongoing record of accomplishments. Describe any collaboration between civilian, DoD, and/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 should be tied to each objective.

- **Study Rationale/Research Gap/Impact. (1-page limit)** Projects should address an important problem or a critical barrier to progress in the field. The study should address a targeted Consortium area of need. All projects 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 study will align with DoD research and clinical goals to maximally benefit SMs and Veterans.

- **Research Methods. (10-page limit)** The overall strategy, methodology, statistical plan, and analyses should be well-reasoned and appropriate to accomplish the specific aims of the project. A sample size estimate must be included and supported by a power analysis or other justification that demonstrates the adequacy of the sample size. If the proposed research includes human subjects, there should be a clear plan for the recruitment of human subjects. Potential problems, alternative strategies, and benchmarks for success should be presented. The proposed research needs to show feasibility for a military or VA setting.

- **Innovation. (1-page limit)** State how the project 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.

- **Research Performance Sites. (1-page limit)** Applicants should describe how the project benefits from unique features of the scientific environment, subject populations, or collaborative arrangements. A description of the study population and location should also be provided.

- **Management Core Collaboration:** When applicable, the PASA Management Core should be meaningfully integrated into the research. The applicant should describe how the PI will integrate the proposed project with the existing PASA Management Core. A teleconference between the PI and the Management Core to determine such arrangements will be held (see your letter of invitation concerning teleconference arrangements).

- **Pharmaceutical Company Collaboration:** Describe any company collaborations that help focus research on compounds that are ripe for further development. A demonstrated relationship with a pharmaceutical company with a path to eventual marketing of the pharmacotherapy will be a factor in the award selections.

- **Human Subject Recruitment and Safety Procedures:** This section should address the following topics:
    - Study Population: Describe the population at the study sites including the approximate number and pertinent demographic characteristics of the population from which participants will be recruited.
    - Inclusion/Exclusion Criteria
    - Description of the Recruitment Process: Describe the methods for identification of potential human subjects (e.g., medical records review, health care provider identification, etc.)

- Description of the Informed Consent Process: (1) Describe who is responsible for explaining the study and answering questions; (2) when and where informed consent will be obtained; (3) address issues of mental capacity
- Screening Procedures: List and describe any evaluations (e.g., laboratory procedures, patient histories or physical examinations) that are required to determine study eligibility.
- Risks and Benefit Assessment

- **Laboratory Animals.** 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.** A budget justification which describe 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. Since PASA project funding is available through a DoD award, all study subaward funds will be subject to policies and restrictions based on the DoD source of this funding. In addition, the full budget must be submitted on the form that will be available on the website: https://pasa.rti.org/About/Grant-Program

- **Quad Chart.** All proposals must include a quad chart (separate from the proposal) briefly describing the study including rationale, population to be studied, sample size, study sites, methods, total budget, and a picture or other graphic describing the study. An example of a CDMRP-compliant quad chart can be found at: https://cdmrp.org/Program_Announcements_and_Forms/

- **Supporting Documentation.** Start each document on a new page with complete header information. ***Include only those components described below; inclusion of items not requested may result in the removal of those items or administrative withdrawal of the application.***

  References Cited: List the references cited in the Research Methods (including URLs if available) using a standard reference format that includes the full citation (i.e., author[s], year published, title of reference, source of reference, volume, chapter, page numbers, and publisher, as appropriate).

  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 or not 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 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.

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 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, 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:

- PI Biographical Sketch (four-page limit)
- PI Previous/Current/Pending Support (no page limit)
- Key Personnel Biographical Sketches (four-page limit each)
- Key Personnel Previous/Current/Pending Support (no page limit)

Forms available on the website: https://pasa.rti.org/About/Grant-Program

C. 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.

D. Submission Due Date and Instructions

All applications must be submitted by e-mail no later than **8:00 PM Eastern Time, March 25, 2016** to:
Jessica Nelson
PASA SRPP Coordinator
PASA_RFA@rti.org
919-485-2733

IV. Application Review and Selection Process

A. Peer Review

To determine technical merit, all applications will be evaluated according to the following areas

Research Strategy and Feasibility:

- How well the scientific rationale supports the project and its feasibility, as demonstrated by a critical review and analysis of the literature, supporting data, and logical reasoning.
- How well the hypotheses or objectives and aims are developed.
- How well the experimental design, methods, data collection procedures, and analyses are developed and support completion of the aims.

- How well the application acknowledges potential problems and addresses alternative approaches.
- 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 the study and the prospect of their participation.
- Whether the research can be completed within the proposed period of performance.
- If applicable, the degree to which the recruitment, informed consent, screening, and retention processes for human subjects will meet the needs of the proposed research and the demonstration of ethical treatment of human subjects.
- If applicable, the degree to which the ethical treatment of animals will be maintained.
- How well the application identifies possible delays (e.g., slow accrual, attrition) and presents adequate contingency plans to resolve them.

- **Statistical Plan**
  - To what degree the statistical model and data analysis plan are suitable for the planned study.
  - How the statistical plan, including sample size projections and power analysis, is adequate for the study and all proposed correlative studies.
- **Impact**
  - How the proposed research study, 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.

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

- **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.

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

C. Award Negotiation

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

V. Post Award Requirements

A. Protocol

Within 30 days of study award, all studies shall submit a detailed study protocol 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. The protocol must be approved by PASA Leadership in writing prior to the initiation of study activities with either human or animal subjects.

B. Study Manual of Procedures (MOP)

In addition to the study protocol, a study manual of procedures (MOP) will be developed by the study team 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 either

human or animal subjects. The content of the protocol shall be similar to the example provided on the PASA website https://pasa.rti.org/About/Grant-Program.

C. Good Clinical Practice (GCP) and Good Laboratory Practice (GLP)

Most studies funded by the PASA Consortium must be conducted in accordance with GCP and/or GLP requirements. Some basic science studies may not require adherence to GLP and a determination will be made concerning GLP in consultation between the PI and the PASA Management Core. The links below provide information concerning these requirements.

GLP:

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

GCP:

http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073122.pdf

http://www.ich.org/home.html

D. 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.

E. Data Elements and Sharing

Applicants are strongly encouraged to incorporate strongly encourages the incorporation of measures from the Core and Specialty collections, which are available in the Substance Abuse and Addiction and Mental Health Research Collection of the PhenX Toolkit https://www.phenxtoolkit.org/index.php into all studies involving human subjects.

The DoD requires that awardees make TBI data generated via this award mechanism available to the research community by depositing de-identified research data into the Federal Interagency TBI Research (FITBIR) Informatics System on a quarterly basis. The FITBIR Informatics system is a free resource to the research community designed to accelerate comparative effectiveness research on brain injury diagnosis and treatment. Data reporting to FITBIR is an opportunity for investigators to facilitate their own research and to collaborate with others doing similar research. While there is no direct charge to users of the FITBIR informatics system, a project estimation tool (https://fitbir.nih.gov/jsp/contribute/fitbir-costs.jsp) is available to help estimate costs and manpower needs that may be associated with data submission. To contribute to FITBIR, rese archers should contact the FITBIR Operations Center ahead of time to arrange for data entry support and to ensure all data have been made compatible with the system. FITBIR guidance and policies, as well as the considerable advantages of FITBIR use to the researcher, are detailed at FITBIR: Federal Interagency Traumatic Brain Injury Research Informatics System http://fitbir.nih.gov/.

FITBIR allows for de-identification and storage of data (medical imaging clinical assessment, environmental and behavioral history, etc.) of various types (text, numeric, image, time series, etc.).

Use of FITBIR's Global Unique Identifier system facilitates repeated and multi-user access to data without the need to personally identify data sources. FITBIR encourages collaboration between laboratories, as well as interconnectivity with other informatics platforms. Such community-wide sharing requires common data definitions and standards.

Data elements must be reported using the National Institute of Neurological Disorders and Stroke (NINDS) TBI Common Data Elements (CDEs) or entered into the FITBIR data dictionary as new, unique data elements. For the most current version of the NINDS TBI CDEs, go to http://www.commondataelements.ninds.nih.gov. Assistance will be available to help the researchers map their study variables to specific CDEs and ensure the formats of the CDEs collected are compatible with the FITBIR informatics system. If the proposed research data cannot be entered in CDE format, the investigators must supply a proposal for an alternative data submission or data sharing vehicle and justification for use. Use of the TBI CDEs is required wherever possible in an effort to create standardized definitions and guidelines about the kinds of data to collect and the data collection methods that should be used in clinical studies of TBI.

F. Other Expectations of Basic Science and Clinical Research Studies

- 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 IRB and USAMRMC 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 a site visit audit, if requested by the GSC.

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 Aim:

- Discovery
- Proof of Concept
- Efficacy Studies

PASA target disorders: (please list all that apply)

- Alcohol
- Opiates
- Marijuana
- Nicotine
- Stimulants
- Other substance
- PTSD
- TBI