

Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium

PASA Study Research Planning Program (SRPP)

Request for Application (RFA) #2: [FY17-Round 1]

Release: December 2, 2016 (Error Revisions: March 24, 2017)

SUBMISSION AND REVIEW DATES AND TIMES

- Pre-Application Deadline 24-March-2017 (by 8:00 PM ET)
- Pre-Application Peer & Programmatic Review April/May 2017
- Notification of Invitation to Submit Full Application 1-June-2017
- Pre full application submission teleconferences June 2-7, 2017
- Full Application Deadline 27-July-2017 (by 8:00 PM ET)
- Peer Review Process & Programmatic Review August/September 2017
- Notification of Award Recommendation 4-Oct-2017
- Award Negotiations October 2017

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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 Research Program. The PASA Consortium goal is funding 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 traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD). 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.

This RFA represents a 2-step process:

- 1) A pre-application submission which is reviewed.
- 2) Subsequent to the review of all the pre-applications, a subset of applicants will be invited to provide full application.

This RFA covers all the requirements for both steps of this process. Please see **Section III** for the details about each step in the process.

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) and the Uniformed Services University of Health Sciences (USUHS). The PASA Consortium Leadership team consists of the Principal Investigator Rick Williams, PhD, from RTI and the co-Principal Investigator Tom Kosten, MD, from BCM.

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.

Additionally, the National Institute of Alcohol Abuse and Alcoholism (NIAAA) and US Department of Veterans Affairs (VA) will 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). 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. Adding these other treatment groups might involve additional therapy process measures or treatment outcomes. In addition depending on relevance to its goals, NIAAA will evaluate supporting highly meritorious proposals that are not able to be supported by PASA for reasons of direct military relevance or limitation of funds. This RFA allows for a one page description of an expanded design that would involve more subjects or costs in order to address known interests of NIAAA or the VA. Note that the VA Office of Research and Development (ORD) operates an intramural program and only funds research conducted by eligible VA-ORD investigators (VHA Handbook 1200.15) at VA medical centers or VA-approved sites and that ORD requires the use of common data elements (<https://www.phenxtoolkit.org/>) for studies of PTSD and/or alcohol/substance use. Applicants interested in consideration of NIAAA co-funding are encouraged to contact Raye Litten at NIAAA (rlitten@mail.nih.gov) and consideration of VA co-funding are encouraged to contact Bob O'Brien at the VA (robert.obrien7@va.gov).

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 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 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. Specifically, the PASA Consortium collaborates with the Recruitment Core of the Center for Neuroscience and Regenerative Medicine (CNRM) at the Uniformed Services University of Health Sciences (USUHS). The Recruitment Core operates at Walter Reed National Military Medical Center, at Fort Belvoir Community Hospital and at various academic locations around Washington. It also has additional contacts at MTFs across the nation and will assist in identifying and recruiting additional sites, particularly MTFs, for the conduct of clinical studies. The Consortium also has contacts at many VA medical centers (VAMCs) that can be used to establish VAMC collaborators and clinical sites to support clinical studies. Additional 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, it is 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 DISCOVER novel medications and combination medications for ASUD.
2. To develop these medications through a rational PROOF OF CONCEPT pipeline model.
3. To test potential medications or medication combinations in PHASE II SAFETY AND PRELIMINARY EFFICACY TRIALS that must be completed within 27-34 months including finalized designs, regulatory approvals and top line analyses. Multiple site studies are encouraged to rapidly recruit optimal target populations and potentially 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 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 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. Phase II Safety and Preliminary 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 this current RFA, we will only be soliciting for Aim 3 studies. Based on the first RFA solicitation for this consortium, 2 discovery and 2 proof-of-concept studies have been approved for funding and are currently ongoing. These studies are assessing single and combination therapy treatments for alcohol use disorder in military populations with concurrent PTSD.

B. Aim 3 - Phase II Safety and Preliminary Efficacy Trials Aim

Phase II safety and preliminary efficacy trials of potential medication combinations in optimal target populations and explore functional genetic polymorphisms for matching patients to these medications. The approach is to use Veterans Health Administration (VHA) medical centers and military treatment facilities (MTFs) to conduct efficient and relatively quickly completed Phase II, placebo controlled,

randomized outpatient pharmacotherapy trials of potential medications or medication combinations in patients with ASUD and concurrent PTSD with or without chronic effects of mild TBI.

The goal of these trials is to determine if there is sufficient evidence of efficacy to support moving forward with formal Phase III clinical trials and if so to inform the study design and sample size needs of the Phase III trial. Outcomes in these trials will include at least: (1) measures of substance abuse such as alcohol use by weekly self-report and breath-alcohol verification for AUD or three-times weekly urine drug screens for other SUD, (2) PTSD symptoms on the Clinical Assessment of PTSD Symptoms (CAPS), (3) treatment retention, and (4) if relevant, TBI symptoms for the corresponding subgroups. Stratification on PTSD severity and when testing combination agents, a 2 X 2 design for the medications (placebo, each drug alone, and both medications combined) are anticipated. The stratification by PTSD will add four more treatment cells for a total of eight cells. As this is a Phase II trial, it will not be formally powered to test for efficacy, however a sufficient number of subjects would be included to allow for preliminary estimates of efficacy across and if possible within PTSD strata. These trials are anticipated to last no more than 27-34 months including planning, regulatory approval and top line analysis and with regard to sample size for, we encourage a probable sample size of 200 (approximately 50 subjects within each treatment group) although all proposals must include a scientifically justified sample size based on power and sample size calculations. We anticipate these Aim 3 studies to have multiple study sites with enough sites to support rapid study enrollment and study completion.

An example of an Aim 3 would be to solicit evaluations of the combined effects of carisbamate and doxazosin for treatment of AUD with or without PTSD. The study design would use a four-armed randomized clinical trial (RCT) to test the constituent drugs alone and in combination while stratifying by PTSD (yes/no) for a total of 8 treatment cells. We hypothesize that the medication combination will yield greatest efficacy as measured by primary (reduced days of heavy drinking) and secondary (treatment retention, abstinent days during treatment, medication compliance, and safety) outcomes for patients with or without PTSD. Those with PTSD who get the combined medications are expected to have the largest reduction in PTSD symptoms on the Clinician Assessment of PTSD Symptoms (CAPS), and reduction in PTSD symptoms will correlate with reduction in alcohol use. We would suggest a single dose based on monotherapy studies of doses that were well tolerated and effective. A multisite recruitment plan should ensure enrollment of the sample size (n=200 for sufficient sample size to obtain treatment effect estimates for four treatment groups across PTSD strata combined) needed to complete the study in an acceptable timeline. This is presented as an example only to illustrate the type and scope of applications anticipated.

III. Submission Information for Pre-Application and Full Application

A. Types of Studies to be Awarded

Type	Period of Performance	Maximum Total Cost
Aim 3. Phase II Safety and Preliminary Efficacy Trials Aim	27 – 34 months	\$3,250,000

Note: Deviations from these time and funding limits will require written permission from PASA Leadership. Additional information will be provided in the letter of request for a full application that you will receive if selected to submit a full application.

B. Pre-application Submission Information

Submission for the PASA FY17 SRPP is a two-step process requiring both (1) a pre-application addressing the specifics described in this announcement, and, if selected for submission, (2) a full application per the details and timeline described in the RFA to be provided with the request for a full application. It is expected that phase II safety and preliminary efficacy trials will be completed with 27-34 months with a budget up to \$3,250,000 total cost. Deviations from these time and funding limits will require written permission from PASA Leadership which can be sought by contacting PASA_RFA@rti.org.

All pre-application components must be submitted by the applying PI. Because the invitation to submit a full 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. PIs and organizations identified in the pre-application should be the same as those intended for the subsequent full application submission.

All pre-applications must include the following elements (as applicable) in the order as listed in this announcement. Failure to include a required element may result in the pre-application not being reviewed.

B.1 Pre-Application Submission Requirements

The pre-application consists of the following components:

Item	Description
Applicant Affiliation(s) and Contacts (No page limit)	List all significant personnel and their affiliations
Pre-application Narrative (3 page limit)	<ul style="list-style-type: none"> <li data-bbox="727 1083 1406 1350">• The Pre-application Narrative page limit applies to text and non-text elements (e.g., figures, tables, graphs, photographs, diagrams, chemical structures, drawings, etc.) used to describe the project. The Pre-application narrative should include the following sections: <li data-bbox="727 1358 1406 1463">• Topic Area: Indicate how the proposed project relates to the PASA aims. <li data-bbox="727 1472 1406 1696">• Research Idea: Clearly articulate the rationale for the project by presenting the ideas and reasoning behind the proposed research; include relevant literature citations and summaries of previous research findings. <li data-bbox="727 1705 1406 1854">• Research Strategy: State the specific aims and objective to be reached. Briefly describe the experimental approach and study design including study arms, approximate sample sizes, and study

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Item	Description
	<p>population.</p> <ul style="list-style-type: none"> • Pharmaceutical Company Collaboration: Describe any company collaborations. • Site Selection and Collaboration: Describe sites planned to be included in the study and their ability to complete the study protocol. Applicants can communicate with the PASA Consortium during the pre-application letter and full application development process to help identify collaborators and a plan for getting sites involved/etc (See Section I.D). • Impact: Describe the impact of the study, especially as it relates to Service members and Veterans. • Estimated Budget and Timeline: Include an estimated total budget and study timeline.
Potential NIAAA and VA Collaborative Support (optional – 1 page limit)	Describe potential study expansions that NIAAA, VA, or both might collaborate and contribute support to the study. This section is optional.
Pre-Application Supporting Documentation	<p>The items to be included as supporting documentation for the pre-application must be provided and are limited to:</p> <ul style="list-style-type: none"> • References Cited: List the references cited (including URLs if available) in the Pre-application Narrative. • List of Abbreviations, Acronyms, and Symbols: Provide a list of abbreviations, acronyms, and symbols used in the Pre-application Narrative. • PI Biographical Sketch (four-page limit per individual): Include a biographical sketch for the PI and co-PI (if applicable) including proposed site PIs for these multisite proposals.

Questions about the pre-application process will be received until February 24, 2017. Answers will be provided on a rolling basis, and after February 24, the PASA Administrator will post a list of all the questions received along with the answers provided.

All final pre-applications must be submitted as a PDF file by e-mail no later than **8:00 PM Eastern Time, March 24, 2017** to:
PASA SRPP Administrator
PASA_RFA@rti.org

B.2 Pre-application Format

All pre-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. Inclusion of URLs in the pre-application to provide additional information is prohibited in all sections.

B.3 Pre-application Screening and Notification Process

Pre-Application Screening Criteria: To determine the technical merits and relevance to the PASA aims, pre-applications will be screened based on the following criteria:

- Alignment with Topic Area: Whether the proposed project relates to the PASA aims.
- Research Idea: How well the research hypothesis or objective is presented. How well the aims/tasks support the hypothesis.
- Research Strategy: How well the research design, methods, and analysis/evaluation strategies anticipated to be used during the research support the research objectives. Whether the proposed approach is supported by prior work and is appropriate in target populations.
- Personnel: How well the PI has formed a transdisciplinary team of scientists and clinical practice stakeholders to work together to test the research hypothesis.
- Pharmaceutical Company Collaboration: How well the PI has formed collaboration with a pharmaceutical company(s) to test the research hypothesis (if applicable).
- Impact: To what degree the proposed work has the potential to inform the study design and sample size needs of future Phase III clinical trials of potential medications or medication combinations in patients with ASUD and concurrent PTSD with or without chronic effects of mild TBI.

Pre-Application Screening Notification: Following the pre-application screening, PIs will be notified as to whether or not they are invited to submit full proposals/applications. Invitations to submit a full application are based on the pre-application screening criteria as published above. The estimated timeframe for notification of invitation to submit a full application is indicated on the title page of this RFA.

C. Invitation to Submit Full Application

Subsequent to the review of all the pre-applications, a select number of submissions will be invited to submit a full application. Responses to participate in this step of the process will only be accepted if you received a letter of notification requesting submission of a full application.

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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.

Questions about the full application process will be received until July 7, 2017. Answers will be provided on a rolling basis, and just after July 7, 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 **8:00 PM Eastern Time, July 27, 2017** to:
PASA SRPP Administrator
PASA_RFA@rti.org

C.1 Full Application Submission Requirements

The full application consists of the following components:

Item	Description
Proposal Cover Sheet	See Appendix A 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

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Item	Description
	<p>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. There should be a clear plan, <u>with demonstrated feasibility</u>, for the recruitment of an adequate number of human subjects in the time frame and from the sites proposed. Potential problems, alternative strategies, and benchmarks for success should be presented. The proposed research needs to show feasibility for a military or VA setting.</p>
Innovation (1 page limit)	<p>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.</p>
Research Performance Sites. (1 page limit)	<p>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 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. Applicants can communicate with the PASA Consortium during the period before the pre-application letter and then during the full application development process for accepted preliminary proposals to help identify collaborators and a plan for getting sites involved/etc (See Section I.D).</p>
Management Core Collaboration (1 page limit)	<p>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).</p>
Pharmaceutical Company Collaboration (1 page limit)	<p>Describe any company collaborations that help focus research on compounds that are ready 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. If the clinical trial involves the use of a drug that has not been approved by the U.S. Food and Drug Administration (FDA) for the proposed investigational use, evidence that an IND application that meets all requirements under the Code of Federal Regulations, Title 21, Part 312 (21 CFR 312) has been submitted or will be submitted to the FDA within 60 days of award is required.</p>

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Item	Description
Human Subject Recruitment and Safety Procedures	<p>This section should address the following topics:</p> <ul style="list-style-type: none"> • 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	<p>**Not applicable for aim 3 studies**</p>
Research and Related Budget and Budget Justification	<p>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. Since PASA project funding is available through a DoD award, all study sub-award 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</p>
Quad Chart	<p>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/</p>
Supporting Documentation	<p>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.</p>
	<p>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).</p>
	<p>List of Abbreviations, Acronyms, and Symbols: Provide a list of all abbreviations, acronyms, and symbols used in the application.</p>

Item	Description
	<p>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.</p>
	<p>Publications and/or Patent Abstracts (<i>three-document limit</i>): 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.</p>
	<p>Letters of Organizational Support (<i>two-page limit per letter</i>): Provide a letter (or letters, if applicable), signed by the Department Chair or appropriate organization official, reflecting the institution’s commitment to the completion of the trial, including laboratory space, equipment, and other resources available for the project.</p>
	<p>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.</p>
	<p>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.</p>
	<p>Research & Related Senior/Key Person Profile: All applications must include:</p> <ul style="list-style-type: none"> o PI Biographical Sketch (<i>four-page limit</i>) o PI Previous/Current/Pending Support (<i>no page limit</i>) o Key Personnel Biographical Sketches (<i>four-page limit each</i>) o Key Personnel Previous/Current/Pending Support (<i>no page limit</i>) <p>Forms available on the website: https://pasa.rti.org/About/Grant-Program</p>

C.2 Full Application Format

All full 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 in the pre-application 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 according to the following areas. For multi-site studies, feasibility, personnel and environment will be evaluated across all sites.

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.
- 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.
- **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.

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 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

V. 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).

VI. 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 measures from the Core and Specialty collections, which are available in the Substance Abuse and Addiction 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, researchers 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 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.

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- 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