Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium

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

Release: June 27th, 2018

SUBMISSION AND REVIEW DATES AND TIMES

• Letter of Intent	22-Aug-18
• Teleconference with PASA Management Core	18-Sep-18
• Full Application Deadline	19-Sep-18
• Peer Review Process & Programmatic Review	24-Oct-18
• Notification of Award Recommendation	31-Oct-18
• Award Negotiations	14-Nov-18

Request for Application (RFA) #3b: [FY18-Round 1]
Synopsis

Full study implementation awards for either:

1. **Conduct of proof-of-principle basic research to determine which compounds are most appropriate for human research trials; or**
2. **Conduct of human proof-of-concept trials with promising compounds.**

The human proof-of-concept trials must be ready-to-implement as defined in Section II.A.

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I. Funding Opportunity Description

A. Introduction

The Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium is funded by the Congressionally Directed Medical Research Programs, CDMRP, (http://cdmrp.army.mil/) as part of its Alcohol and Substance Abuse Disorders Research Program (ASADRP) from the FY14 and FY17 ASADRP consortium awards (W81XWH-14-ASARP-CA and W81XWH-17-ASADRP-CA). The PASA Consortium goal is to fund study applications for developing new medications that can be brought to therapeutic use to improve treatment outcomes for alcohol and substance use disorders (ASUD), especially as related to post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI). Studies of military and Veteran populations are encouraged. These medications will ideally address the comorbidity between ASUDs and posttraumatic stress disorder (PTSD), because this comorbidity is common in a military population along with mild to moderate traumatic brain injury (TBI). Alcohol use disorder (AUD) is the most common ASUD in the military, but opiate use disorder (OUD) also has developed significant clinical importance due to prolonged pain treatments with opiates. Since both ASUD and PTSD have FDA approved pharmacotherapies, one logical starting point for treating this comorbidity might be to augment or combine these agents. The approved agents for ASUD are disulfiram, acamprosate and naltrexone in either an oral and long acting injection formulation. For OUD approved agents are methadone, buprenorphine and naltrexone. For PTSD two serotonin reuptake inhibitors, sertraline (Zoloft®) and paroxetine (Paxil®), are FDA approved pharmacotherapies. While TBI is of interest, it has no FDA approved specific pharmacotherapies, and none of these combined disorders have FDA approved pharmacotherapies. Commercialization linked to FDA approval for these new medications or combinations of medications is critical so that early linkages to pharmaceutical companies are considered strengths of any application for PASA funding.

The PASA SRPP is requesting applications for (1) basic research to determine compounds most appropriate for human research trials; and (2) ready-to-implement human proof-of-concept trials. Human research trials must have an established protocol and FDA approval for the study.

B. Program Description

The PASA Consortium is administered by a Management Core led by RTI International (RTI) in collaboration with the Baylor College of Medicine (BCM). The PASA Consortium Leadership team consists of the Principal Investigator Rick Williams, PhD, from RTI and the co-Principal Investigators Tom Kosten, MD, from BCM and Tracy Nolen, DrPh, from RTI. Oversight of the Consortium is provided by a Government Steering Committee (GSC) assembled by the CDMRP.

The goal of the PASA Consortium is to fund study applications for developing new medications that can be brought to therapeutic use to improve treatment outcomes for ASUD, especially as related to PTSD and TBI. These medications will ideally address the comorbidity between ASUDs and PTSD. Clinical trials that include military Service member (SM) and Veteran populations are highly desirable because this comorbidity, along with mild to moderate TBI, is common in these populations.

C. The Management Core

The Management Core is responsible for soliciting and prioritizing applications. Successful applications will be selected by a Government Steering Committee formed by the U.S. Department of Defense. The Management Core will provide oversight and coordination for future proof-of-principle basic research studies and proof-of-principle human clinical trials supported by the Consortium. The

Management Core will provide the administrative, protocol development and review, regulatory, statistical, resource, and data management/storage functions necessary to facilitate rapid development of research that would perhaps not otherwise be feasible without the Consortium approach. The Management Core contains multidisciplinary expertise and experience in support of ASUD research. The Management Core will coordinate the regulatory strategy for FDA compliance, in collaboration with the industry sponsor, leading to potential product development and licensing. Additional information about PASA is available on its website: https://pasa.rti.org/.

D. Expert Advisers

In addition to the Management Core, the following are available for consultation:

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

NIAAA and VA are available to provide consultation, guidance and expertise on the design, conduct and analysis of relevant clinical studies evaluating potential medications for treatment of PTSD-Alcohol Use Disorders. In addition, depending on the relevance of the proposed studies to the current medication development goals of the NIAAA and VA, and on the availability of funds, the NIAAA and VA will consider contributing support to responsive, meritorious application(s) if the study is ultimately approved to move forward. For example, the NIAAA might consider expanding the populations being studied beyond Service Members and Veterans by funding additional civilian sites. Similarly, the VA might consider expanding the number of VA sites by funding those sites to provide more subjects for comparisons involving behavioral interventions such as progressive exposure therapy or active medications such as to paroxetine. Applicants interested in consideration of NIAAA co-funding are encouraged to contact Dr. Raye Litten at NIAAA (rlitten@mail.nih.gov) and consideration of VA co-funding are encouraged to contact Dr. Katrina Foster at the VA (Katrina.Foster@va.gov).

E. Study Sites with Military and Veteran Focus

Applications should address topics with a focus on military 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. The Consortium also has contacts at many VA medical centers (VAMCs) and military treatment facilities (MTFs) that can be used to establish collaborators and clinical sites to support clinical studies. Additional information concerning such collaborationscan be obtained by contacting PASA_RFA@rti.org.

F. Pharmaceutical Company Participation

Obtaining FDA approval for a pharmacotherapy usually is facilitated by partnership with a pharmaceutical company for Phase 3 testing and eventual New Drug Application (NDA). While developing such a commercial partnership may not be possible for all the studies to be funded by the PASA SRPP, it is strongly recommended that such a commercial partner be obtained as early in the medication development process as possible. PASA Leadership has recruited several interested commercial partners with potential compounds to test. A discussion of these potential compounds for use can be arranged by contacting PASA_RFA@rti.org. A demonstrated relationship with a

pharmaceutical company with a path to eventual marketing of the pharmacotherapy will be a factor in the award selections.

II. Research Focus

A. Research Aim

The PASA Consortium has three broad aims:

1. To identify promising compounds
2. Conduct proof-of-principle basic research to determine which compounds are most appropriate for human research trials; and
3. Conduct human proof-of-concept trials with promising compounds.

For this RFA, we are soliciting for research grants under basic science research studies (Aim 2), and ready-to-implement human proof-of-concept trials (Aim 3).

For the Aim 3 trials, the application will need to demonstrate both:

1. A ready to implement protocol has been prepared that will require only minor modification to implement within the PASA Consortium without an extended planning period.
2. That an Investigational New Drug (IND) application has been approved by the U.S. Food and Drug Administration (FDA) for the trial (IND exemption by the FDA is acceptable), or that an IND has been submitted to the FDA by the due date of the application. Deviations from this requirement will require written permission from PASA Leadership prior to submitting the application. Please contact PASA_RFA@rti.org including a summary of FDA communications concerning the trial.

If the trial is not ready-to-implement, then application for a planning grant under the companion PASA Planning Grant RFA should be made. The planning grant could be used to work with the PASA Management Core to finalize an IND submission to the FDA.

B. Basic Research

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. PASA currently funds 2 basic research studies, details can be found here: https://pasa.rti.org/Research-Studies.

C. Human Proof-of-Concept Trials

Human proof-of-concept may be either Phase 1 or Phase 2 clinical trials. Examples of studies of potential compounds should involve small numbers of subjects and include assessment of medical safety in ASUD humans and of potential doses for efficacy in humans with ASUD, PTSD and possibly TBI. The studies can range from Phase 1 through late Phase 2 including, for example,

- drug/substance safety interaction studies and PK studies, especially when the compound has not previously been co-administered with the substance of abuse (such as alcohol)
- dose finding studies,
- multisite safety and preliminary efficacy trials intended to show sufficient evidence of efficacy for a future Phase III clinical trial.

Phase 1 Trials

Phase 1 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.

Phase 2 Safety and Preliminary Efficacy Trials

Phase 2 involves 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 2, 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 3 clinical trials and, if so, to inform the study design and sample size needs of the Phase 3 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 2 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. With regard to sample size, 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 Phase 2 studies to have multiple study sites with enough sites to support rapid study enrollment and study completion.

III. Submission Information

A. Types of Studies to be Awarded

Type	Period of Performance	Maximum Total Cost
Basic Research	12 months	$275,000
Phase 1 Trials	18 - 24 months	$700,000
Phase 2 Safety and Preliminary Efficacy Trials	28 – 32 months	$3,000,000

Note: 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 until August 22, 2018 by email to PASA_RFA@rti.org. Answers will be provided on a rolling basis, and just after August 8, 2018, the PASA Administrator will post on the PASA website a list of all the questions received along with the answers provided.

B.1 Letter of Intent and Pre-submission Teleconference

A letter of intent (LOI) must be submitted prior to submission of the full application. Early submission of the LOI will be greatly appreciated. The LOI shall not exceed 4 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 email address of the PI;
- A brief overview of the study including research aims and objectives;
- The status of the IND submission to the FDA concerning the trial; and
- A list of the sites where the study will be conducted.

The PASA Management Core will contact the PI to set up a pre-submission teleconference with the PI and his/her study team. The purpose of the teleconference is to explain the support available from the Management Core in the conduct of a study and to determine a plan for the activities to be conducted by the study team and the Management Core to guide the preparation of the application.

B.2 Full Application Submission Requirements

All final applications must be submitted as a PDF file by e-mail no later than 11:59 PM Eastern Time on **September 19, 2018** to:
PASA SRPP Administrator
PASA_RFA@rti.org

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 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. For a human clinical trial, there should be a clear plan, with demonstrated feasibility, 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.
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.

Item	Description
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 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.
Management Core Collaboration (1 page limit)	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 pre-submission teleconference between the PI and the Management Core to determine such arrangements will be held.
Pharmaceutical Company Collaboration (1 page limit)	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 a clinical trial is proposed that requires approval 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 approved or will be submitted to the FDA prior to the due date of the application must be included.
Human Subject Recruitment and Safety Procedures (human clinical trials only)	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 (basic science studies only)	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

Item	Description
	used to ensure that the experiment does not unnecessarily duplicate previous research
Research and Related Budget and Budget Justification	A budget justification which describes the labor and other direct costs necessary to complete the project must be included here. The budget should reflect yearly direct costs for each year over the entire period of performance. 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
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

Item	Description
	that will demonstrate that the PI has the support or resources necessary for the proposed work. Letters of support from a collaborating pharmaceutical company are welcomed and desired.
	Letters Confirming Access to Military or VA Patient Populations or Resources (if applicable): If the proposed research plan involves access to active duty military and/or VA patient populations or resources, include a letter of support, signed by the lowest ranking person with approval authority, confirming such access. If access cannot be confirmed at the time of application submission, the Government reserves the right to withhold or revoke funding until the PI has demonstrated support for and access to the relevant population(s) and/or resources.
	Research & Related Senior/Key Person Profile: All applications must include: **o** PI Biographical Sketch (*four-page limit*) o PI Previous/Current/Pending Support (*no page limit*) o Key Personnel Biographical Sketches (*four-page limit each*) o Key Personnel Previous/Current/Pending Support (*no page limit*) Forms available on the website: https://pasa.rti.org/About/Grant-Program

B.3 Full Application Format

All applications should be submitted as a single PDF file, except for the full budget PDF form which should be a separate file. All text should be in Calibri with a font size of no less than 11. All margins should be at least one inch. Inclusion of URLs to provide additional information is prohibited in all sections.

IV. Full Application Review and Selection Process

A. Peer Review

To determine technical merit, all applications will be evaluated by a peer-review committee according to the following scored criteria which are of equal importance. For multi-site studies, feasibility, personnel and environment will be evaluated across all sites.

Research Rational, Strategy and Feasibility:

- How well the scientific rationale supports research on the proposed compound for treatment of ASUD comorbid with PTSD and/or TBI. The feasibility of such research, as demonstrated by a critical review and analysis of the literature, supporting data, and logical reasoning.
- How well the application describes existing pre-clinical and clinical trial research of the proposed compound and justifies additional study for treatment of ASUD comorbid with PTSD and/or TBI.

- How well the application acknowledges potential problems or delays and addresses alternative approaches and solutions.
- If applicable, how well the application provides evidence of availability of and access to the necessary study populations and/or resources.
- If applicable, how well the PI addresses the availability of and access to SMs and/or Veterans for any subsequently funded clinical trials and the prospect of their participation.
- How well the application assesses the likely next steps needed for continuing the compound along the regulatory pathway.
- Whether the investigators demonstrate an ability via pharmaceutical collaboration or otherwise for compound to continue to progress long term on regulatory pathway.

- **Impact**
  - How the proposed research, if successful, will:
    - Promote greater understanding of the treatment of ASUD, PTSD and/or TBI
    - Promote the development of improvements in pharmacotherapies for ASUD, PTSD and/or TBI
    - Support potential approval and marketing of pharmacotherapies for ASUD. PTSD and/or TBI.
- **Personnel**
  - How the background and expertise of the PI(s) and other key personnel demonstrate their abilities to perform the proposed work.
  - How the levels of effort by the PI(s) and other co-investigators are appropriate to ensure the successful conduct of the project.
  - How the PI(s)'s and co-investigators' record(s) of accomplishment demonstrate their abilities to accomplish the proposed work.
- **Environment**
  - How the scientific environment is appropriate for the proposed research.
  - How the research requirements are supported by the availability of and accessibility to facilities and resources.
  - How the quality and extent of organizational support are appropriate for the proposed research.
- **Transition Plan**
  - Whether collaborations with industry and/or other institutions exist that will be used to provide continuity of development to inform study design, sample size and dosing for future clinical trials.

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

- **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 Programmatic Review of applications will be made by the PASA Management Core and the GSC. The GSC will make funding recommendations using the following criteria:

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

Final selection of research grants will be made by the Government Steering Committee

V. Award Negotiation

If your application is recommended for funding by the GSC, 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 develop a protocol in conjunction with the Management Core and submit for review and approval by the PASA Leadership and the GSC. The content of the protocol must follow the PASA Protocol Template 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, in conjunction with the Management Core and submitted to the PASA Leadership for review and approval. The MOP must be approved in writing by the PASA Leadership prior to the initiation of study activities with either human or animal subjects. 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

C. 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.

D. 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.

E. 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.
    - 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