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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The goal of the PASA Consortium is to fund research that aims to identify and develop new medications to improve treatment outcomes for alcohol and substance use disorders (ASUD), especially those that occur concurrently with traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD). In the fifth year, the consortium completed activities in support of RFA #4. Manuscript development for PT150 Alcohol Interaction study and 2 pre-clinical studies were initiated. The Davis and Petrakis study protocol continued enrollment. The PK study began preparation activities in anticipation of study launch.

15. SUBJECT TERMS
None listed.

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1. Introduction

The goal of the PASA Consortium is to fund research that aims to identify and develop new medications to improve treatment outcomes for alcohol and substance use disorders (ASUD), especially those that occur concurrently with traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD). Clinical trials that include military service member and Veteran populations are highly desirable because these comorbidities are common in these populations. 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. FDA approved pharmacotherapies are available for ASUD, OUD, and PTSD. While TBI is of interest, it has no FDA approved specific pharmacotherapies, and none of these combined disorders have FDA approved pharmacotherapies. Under a Cooperative Agreement, RTI International is partnering with the CDMRP to solicit, select, and operationalize research studies that support the goals of the PASA Consortium.

The PASA Consortium has three aims under the primary objective to develop medications to treat ASUD in the context of the reciprocal relationship between ASUD, the physiological state of stress, and the subjective state of anxiety as manifested in PTSD or TBI. The three broad aims are:

AIM 1. Discover novel medications and combination medications for ASUD

AIM 2. Develop these medications through a rational Phase I proof of concept pipeline

AIM 3. Conduct Phase II preliminary safety and efficacy trials of potential medication combinations in optimal target populations and explore functional genetic polymorphisms for matching patients to these medications.

The subject of the Core research program in Houston at Baylor and the Michael E. DeBakey VA Medical Center (MED VAMC) is to help facilitate the issuing of Requests for Research Applications (RFA) on an approximately yearly basis, with the primary goal of providing new medications for substance use disorders (SUD) with comorbid Post-Traumatic Stress Disorder (PTSD) and/or mild Traumatic Brain Injury (mTBI). The purpose of these proposals should fit within three categories of work:

1. Pre-clinically to discover medications using animal models of SUD, PTSD and/or mTBI.

2. Clinically to test medications which have completed FDA Phase 1 safety testing, in small human studies for safety and some surrogate efficacy measure (e.g. fear potentiated startle for PTSD, drug choice vs money for SUD) in the SUD patient's.

3. Larger outpatient clinical trials for late Food & Drug Administration (FDA) Phase 2 multi-site randomized, placebo-controlled clinical trials for proof and concept of efficacy.

Submitted proposals are then evaluated, including planning grants for the larger clinical trial proposals, in order to ensure feasibility. The feasibility assessment is based on novelty, statistical power, subject availability, study design, and scientific significance aligned with stated specific aims and purpose of the proposal. This is an extensive process and includes biweekly conference calls with the RTI Core resources over several months. During this planning, the scope of the research and its trajectory for commercialization through industry collaboration is assessed and facilitated

though discussions of FDA regulatory requirements and the capacity of the pharmaceutical partner to provide the support needed. Expected levels of support minimally include, provision of medications and placebos, investigator initiated Investigational New Drug (IND) filing by citing IND files of the company, and related follow-through to Phase 3 studies and Non-Disclosure Agreements (NDA) filings, if these PASA-DoD studies are successful.

2. Keywords

- alcohol and substance use disorders
- post-traumatic stress disorder
- traumatic brain injury
- pharmacotherapy
- research consortium

3. Accomplishments

3.0 PASA Core

In Year 6, the PASA Core research program continued activities related to management and oversight of ongoing animal and clinical studies.

3.0.a Primary objectives and milestones for the sixth year were:

A primary objective of the Core is to efficiently manage and monitor studies that lead to accurate, quality data for publication and dissemination. This is achieved though core management responsibilities such as regularly scheduled check-in meeting, routine follow-up on action items and study issues of critical importance, ensuring data accountability, performing and assisting with statistical analysis, engaging in quality control and assurance activities, and other activities pertaining to overall study management and oversight. The Core has worked directly with each project in fine-tuning, clarifying, and adjusting study endpoints as dictated by planned outcomes as well as interim data analysis findings. Another objective of the Core is to ensure the PASA website remains a living entity with regular and timely updates for all active studies.

Consistent with the 3 primary program objectives noted in the Introduction (Section I), the overall focus of the Core project is in (i) providing assistance in establishing priorities and endpoints for each project; (ii) providing scientific guidance in achieving project goals; and (iii) facilitating the navigation of challenges incurred in study conduct toward successful and timely completion. In FY21, the Consortium maintained a continued focus on tracking of COVID-19 barriers and delays. The impact of COVID-19 did result in delays with respect to prespecified study goals in FY21. This was particularly the case for Aims 2 and 3 for late Phase 1 and Phase 2 clinical studies that required human subjects' interaction. Preclinical Aim 1 studies also incurred delays due to temporary closure of some animal laboratories and restrictions with respect to the number of personnel permitted in the laboratory at the same time, leading to staggering of shifts and reducing lab time to between 2 to 3 days per week. The PASA core ensured close communication with all research sites and tracked status through shared internal documentation.

3.0.b Accomplishments under the goals include:
Consistent with the afore-referenced goals and objectives, the Core has worked directly with each project in fine-tuning, clarifying, and adjusting endpoints as dictated by planned outcomes as well as interim data analysis findings. Examples of the most significant accomplishments over the course of this fiscal period include the following:

- Convened for 3 DSMB meetings to review active studies.
- Maintenance of Consortium and study progress despite the COVID-19 pandemic (i.e. continued to remotely site monitor, stayed in close communications with and tracked sites' abilities to continue with study activities, revised protocols and submitted to regulatory entities to allow for telemedicine endeavors, etc.).
- Routine updating and maintenance of the PASA website for PASA 1 studies.
- Publication of 1 pre-clinical article by Dr. Haile in the evaluation of the GABAB receptor positive allosteric modulator ASP8062 reduces operant alcohol self-administration in male and female Sprague Dawley rats in the journal *Psychopharmacology*.
- Publication of 1 manuscript by Dr. Verrico's evaluation of PT150 (Formerly ORG34517) as a Potential Treatment for Alcohol Use Disorder – Alcohol Interaction Study in the journal *Scientific Reports*.
- Over this past fiscal year, in an effort to facilitate subject recruitment across PASA sites, Drs. Kosten and Domingo engaged with the leads of several veterans' groups in Houston. These groups have chapters across the country and expressed an interest in facilitating recruitment into the various available PASA research studies.

3.0.c Training and professional development provided:
The RTI data coordinating center staff performing study related activities on the PASA Consortium are responsible for complying with training requirements set forth by RTI and federally mandated regulations. All RTI staff performing study related activities on the PASA Consortium train on the PASA and BiostatEpi Division standard operating procedures (SOPs). Exceptions to this requirement are for staff who solely manage the PASA website and manage the financial/subcontracting processes. Individual staff are responsible for providing clearly labeled documentation of relevant training files for PASA. PASA core calls are also a space dedicated to checking-in on study progress and development for RTI staff.

For study site staff, the PASA consortium ensures personnel are adequately trained on all pertinent study documents including but not limited to the study protocol, manual of procedures (MOP), electronic data capture system (EDC), and all other applicable study materials. This is completed through meeting or communicating with the site study staff and having them acknowledge their participation in review of key study resources.

Due to the restrictions attributed to COVID-19 all training and professional development activities as described above were completed virtually.

Dr. Kosten's unique position within the Michael E. DeBakey VA Medical Center (MEDVAMC) allows for his direct involvement in sponsoring non-VA trainees/employees through the VA's HR processes. Navigating these internal VA hiring processes helps to provide the necessary support and vetting for non-VA employees' engagement in research on federal VA premises. A most

recent effort has been the inclusion of VA-based staff RNs and PAs in facilitating medical procedures in human trials requiring medically credentialed personnel. Currently, these efforts are underway at the VA Medical Center in Houston, but it is expected that this could form a template for other participating sites within the overall PASA Consortium. This engagement also necessitates completion of multiple research related trainings throughout the year with typically annual refresher courses in the protection and safety of human subjects in research, HIPAA (Health Insurance Privacy and Accountability Act), Privacy and Information Security Awareness, Biosecurity training; to name but a few. These trainings largely occur in an online environment and have continued undisrupted for all research personnel and under the supervision of Dr. Kosten.

3.0.d Dissemination to communities of interest:
The PASA Consortium currently hosts a website [https://pasa.rti.org/] that houses both public and private portals. The private side of the website is password protected and can only be accessed by PASA-funded study researchers. Study specific templates, tools, dashboards, and trackers are disseminated via the private side of the portal. The public side of the website functions to provide members of the public with study-related information and background and serves as a mechanism for making resources, updates, and opportunities specific to the Consortium available to the general public.

Annually, the PASA Consortium investigators present various PASA projects at the Congressionally Directed Medical Research Programs (CDMRP) hosted Military Operational Medicine Research Program (MOMRP). Two days in September 2021, MOMRP hosted an Alcohol and Substance Use Virtual IPR in which a select few of the PASA investigators presented.

The PASA Core also helps in dissemination of study data through collaboration on the development and submission of study specific manuscripts to relevant high-impact scientific journals. The PASA Core personnel provide support in the development and/or finalization of all manuscripts, including performing required statistical analyses. Once manuscripts are published, the Core highlights publications via the public website.

3.0.e Plans for next reporting period to accomplish goals and objectives:
Over the next reporting period, Consortium leadership will continue to provide comprehensive and quality support to currently funded studies. Other areas of focus include collaboration with study teams in the development of scientific manuscripts and submissions to relevant high-impact journals. Additionally, the Core will continue to seek out and employ innovative strategies for identifying and recruiting eligible participants for inclusion across active studies. One example includes considering nearby non-VA psychiatric facilities who service veterans and engaging their assistance in helping to recruit/advertise the study to their patient populations. Additionally, there are ways in which the phone screen process might be expanded upon to increase the ready cohort of participants available for in-person screening.

3.1 AS140026-A2 Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol Use Disorder

3.1.a Primary objectives and milestones for the fifth year were:

- Finalize Manuscript
- Publication

3.1.b Accomplishments under the goals include:

The study team finalized the manuscript and published in the journal *Psychopharmacology.*

3.1.c Training and professional development provided:

None.

3.1.d Dissemination to communities of interest:

The team has published study data. It has been disseminated to communities of interest through publication.

3.1.e Plans for next reporting period to accomplish goals and objectives:

Study has concluded, no additional goals.

3.2 AS140026-A3b PT150 (formerly ORG 34517) as a Potential Treatment for Alcohol Dependence – Alcohol Interaction Study

3.2.a Primary objectives and milestones for the fifth year were:

- Finalize Manuscript
- Publication

3.2.b Accomplishments under the goals include:

The study team finalized the manuscript and published in the journal *Scientific Reports.*

3.2.c Training and professional development provided:

No training or professional developed was needed due to study conclusion.

3.2.d Dissemination to communities of interest:

The team has published study data. It has been disseminated to communities of interest through publication.

3.2.e Plans for next reporting period to accomplish goals and objectives:

Study has concluded; no additional goals.

3.3 AS140026-A3c Effects of Ethanol on the Pharmacokinetics of PT-150 (Formerly ORG34517)

The primary purpose of this Phase I, single center drug study is to evaluate the safety and tolerability of PT150 in combination with alcohol and to determine the amount of PT150 and alcohol in blood (i.e., the pharmacokinetic (PK) interactions between alcohol and PT150) in 10 non-treatment seeking participants.

Participants will undergo 10 days of in and out-patient visits while enrolled in the research study. On Day 2, the first dose of study drug (PT150) will be given in the amount of 900 mg. The study drug will continue to be given in the amount of 900 mg and administered daily thereafter at approximately 8 AM for the next five days (through study Day 7). Study Day 6 marks the start of the PK assessment phase for

PT150 without alcohol, which will continue through Day 7. Day 7 also marks the first day of the PK assessment phase for PT150 with alcohol, which will continue through Day 9. On Day 9, the PK assessment phase for PT150 with alcohol will conclude, and participants will be discharged after collection of health and safety measures. The study aligns with PASA aims for a proof-of-concept study to assess safety and surrogate markers (extinction learning) of clinical efficacy in PTSD for treatment with an existing drug compound in veterans with AUD combined with PTSD. The medication is novel and innovative, and the mechanism of action (GR antagonism) for treatment of the key symptoms/behaviors is supported by previous research, including two clinical trials currently underway (PTSD in veterans, AUD is non-veterans) using a drug with a similar mechanism of action. The efficacy is likely via modulation of the stress-axis, which is a logical target for the PTSD+AUD population.

3.3.a Primary objectives and milestones for the sixth year were:

The primary objective includes assessing if measures of concentration and timing of PT150 levels in the blood differ between the PT150 challenge (challenge on Day 8 and continually observed through Day 9) in combination with alcohol (ethanol beverage) compared to the steady-state PT150 challenge, absent alcohol challenge, on Day 7.

Secondary objectives are to determine if measures of concentration and timing of BAL in the blood differ between the active alcohol challenges only (Day 1/baseline) and PT150 challenges in combination with alcohol challenges (Day 8). Other secondary outcomes include evaluating health and safety outcomes as well as withdrawal from alcohol.

Administrative goals for the year include implementation of the study protocol, with a goal to complete recruitment in February of 2022. The research team is working to onboard new personnel as quickly as possible.

3.3.b Accomplishments under the goals include:

A fully executed CRADA was granted on 12-APR-2021. MOP finalization was initially completed on -17-MAR-2021, with additional changes being made and a second round of finalizations completed on 19-MAR-2021. Specimen shipment training for staff coordinators was completed on 01-MAR-2021. PK label testing was completed on 26-APR-2021. PT 150 recertification occurred on 20-MAY-2021, extending the use of the study medication for an additional 2 years. Following the execution of the CRADA between RTI and Baylor College of Medicine (BCM), the research team opened research coordinator I and II positions. In addition, the site has been working hard to hire nursing/phlebotomy staff who are capable of performing the numerous blood draws required by the study protocol. Hiring has been a challenge due to VA administrative and operational issues, but continues in earnest, and the research team continues to look for additional staff who meet the qualifications of the intended roles.

3.3.c Training and professional development provided:

Baylor College of Medicine and the MEDVAMC regularly provide training courses for research personnel. Trainings seminars at Baylor College of Medicine are conducted by the Office of Research and Sponsored Programs Office and are SoCRA approved training programs.

3.3.d Dissemination to communities of interest:

There are no results to disseminate currently since data collection is still ongoing.

3.3.e Plans for next reporting period to accomplish goals and objectives:

The team anticipates commencement of the study by November 2021. Study coordinators will undergo off-site training to assist with the collection and handling of PK samples. Additional certifications will be administered by the study physician, Dr. Kosten, to ensure venous draws conducted on subjects fall within full compliance with all prevailing VA safety standards. The study team has generated a cumulative list of interested research subjects from which to recruit. Once the study is in the field, those subjects will be contacted and screened for enrollment.

3.4 AS140026-A5 Kappa Opioid Receptor Antagonism for the Treatment of Alcohol Use Disorder and Comorbid PTSD

There is an urgent need for more effective treatments for alcohol use disorder (AUD) and post-traumatic stress disorder (PTSD), given the grave personal suffering, enormous societal economic burden, and known serious complications caused by PTSD and AUD, especially if left untreated or unremitting. The use of medications that result in kappa opioid receptor (KOR) antagonism represents a novel potential treatment for Veterans and Service Members with comorbid AUD and PTSD. KOR antagonists are being developed by the pharmaceutical industry, but until available for investigator-initiated trials, the combination of buprenorphine and naltrexone allows for a proof-of-concept study until a formulated KOR-antagonist becomes commercially available.

Buprenorphine acts as an antagonist at kappa and partial agonist of the mu receptors, and naltrexone blocks the mu receptor, which in combination yields a pharmacological net effect of a KOR antagonist. The use of buprenorphine in a non-opioid dependent population has ethical implications given its risk of addiction, which has led to the idea to combine it with naltrexone in order mitigate the potential for misuse. Further, preclinical studies suggest KOR antagonism is important for drinking behavior, stress induced reinstatement of drug and alcohol consumption. Clinical studies have shown that KOR antagonists have therapeutic effects in treatment-resistant depression compared to placebo. For these reasons, there is substantial interest in the development of KOR antagonists for indications such as AUD and PTSD.

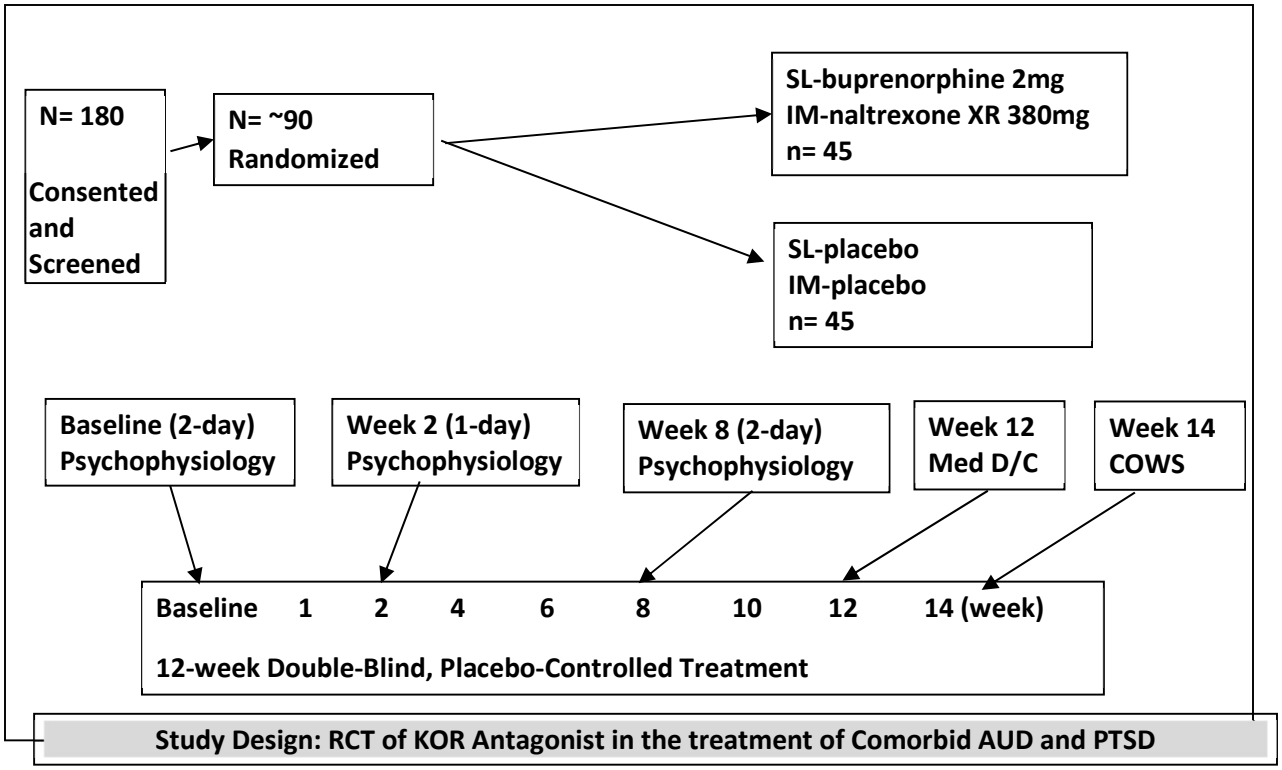

Figure 1: Study Design. Provides an overview of the current study design, which is a parallel, multi-site, placebo-controlled 12-week trial of the combination of sublingual buprenorphine (2mg/d) and extended-release injectable naltrexone (Vivitrol; 380mg/month).

3.4.a Primary objectives and milestones for the fifth year were:

The over-arching objective of this study is to evaluate the efficacy and physiological effects of sublingual buprenorphine (SL-BUP; Subutex) combined with extended-release injectable naltrexone (XR-NTX; Vivitrol) in the treatment of comorbid AUD and PTSD.

Aim 1: To evaluate the efficacy of SL-BUP + XR-NTX in the treatment of comorbid moderate-to-severe AUD and PTSD based on a response in both AUD and PTSD outcomes.

Aim 2a: Examine the baseline association between fear extinction and PTSD symptom severity in participants with comorbid AUD and PTSD.

Aim 2b: Examine the baseline association between Psychophysiological Reactivity to a Trauma-Relevant Stimuli and PTSD symptom severity.

Aim 2c: Examine the baseline association between Psychophysiological Reactivity to Alcohol-Cues Stimuli and measures of alcohol craving.

Aim 3: Examine the association of baseline fear extinction, stress reactivity, and treatment outcomes.

Aim 4: Examine whether the degree of change from baseline to 2-week psychophysiological measures are associated with AUD and PTSD outcomes at week 8. An early indication of signal detection can be used in the future to enhance precision medicine treatment decisions.

3.4.b Accomplishments under the goals include:

Goal #1: Post-COVID pandemic re-opening of enrollment and maintain staffing.

The COVID-19 pandemic had sites closed for the second half of FY20, thus, the first foal of FY21 was to re-open sites for enrollment. The Tuscaloosa (Davis) and West Haven (Petrakis) sites were ready to re-open enrollment at the beginning of FY21 (OCT-2020) and the Detroit site (Norrholm) was approved within the first quarter of FY21 after a virtual site visit was held on 11-NOV-2021. Sites operated using COVID-19 safety measures, including the following: vaccinate employees and study team members, vaccinate as many veterans as possible, minimize in-person visits, wear face masks, maintain social distancing, decontaminate high touch surfaces, limit capacity in clinic at any one time, and continue to place hold on high-risk procedures, such as breathalyzers (blood alcohol level instead) and psychophysiological assessments.

Tuscaloosa site experienced staff turnover in first quarter FY21 and two replacement coordinators and one independent evaluator joined the team and were trained quickly. The lead Research Coordinator and the back-up Coordinator at the Tuscaloosa site accepted another position as of 24-SEPT-2021 and the positions are being advertised for backfill. Birmingham satellite site remains active as a recruitment site for the Tuscaloosa VA, but since all in-person visits must be conducted at the neighboring Tuscaloosa VA site, the study participants are consented and evaluated at the Tuscaloosa VA.

West Haven site resources remain stable, and a back-up research coordinator was trained during 4th quarter to work fulltime during the primary coordinator's upcoming maternity leave. Detroit site did not meet recruitment goals for the first 6 months of FY21. Due to continued lagging enrollment at the Detroit site (i.e., only one participant was enrolled at the end of the 2nd quarter FY 21), the Detroit site was closed to enrollment at in JUN-2021 and their subaward ended 30-JUN-2021. A new subaward for only Dr. Norrholm's time for the psychophysiological assessment data analysis and interpretation was issued in JUL-2021. A smaller subaward to support minimal effort for Dr. Norrholm to conduct the training on psychophysiological assessments and data analysis was put into place for the Detroit site for the remaining duration of the study. Study drug provided to the Detroit site by Alkermes is to be destroyed as directed by Alkermes. KOR Antagonist Placebo SL tabs provided by Tonix were shipped to the Tuscaloosa site 10-SEPT-2021.

Budget reallocation: The Detroit budget was reallocated to the Tuscaloosa site to support the expanded recruitment into the Central Alabama VA Healthcare System starting 01-JUL-2021. In addition, the budget was restructured to allow for a no-cost extension at the Tuscaloosa and West Haven sites in FY22.

GOAL #2: Randomize n=100 (n=90 in the two remaining study arms) and retain ≥70% of randomized sample at the 8-week primary endpoint.

Although enrollment was open, COVID-19 pandemic still had a major negative impact on enrollment since most care was still being delivered via telehealth modalities and participants were reluctant to participate in a clinical trial due to having to come to the medical centers

during 1st and 2nd quarter of FY21. A commercial recruitment platform, TrialFacts, was launched in NOV-2020 and generated referrals to all study sites, but many of these referrals were pre-screen failures or not responsive to outreach. Assertive recruitment via letters to list of VA patients who had diagnosis of AUD or PTSD was maintained during FY21, including expanding recruitment to Central Alabama VA Health Care System as of MAY-2021. The Detroit VA did not approve the site PI at Wayne State to mail recruitment letters to veterans, which substantially impacted recruitment at the Detroit site. In FY20 and additionally in FY21, protocol amendments were made to reduce barriers to recruitment and reduce sample size requirements.

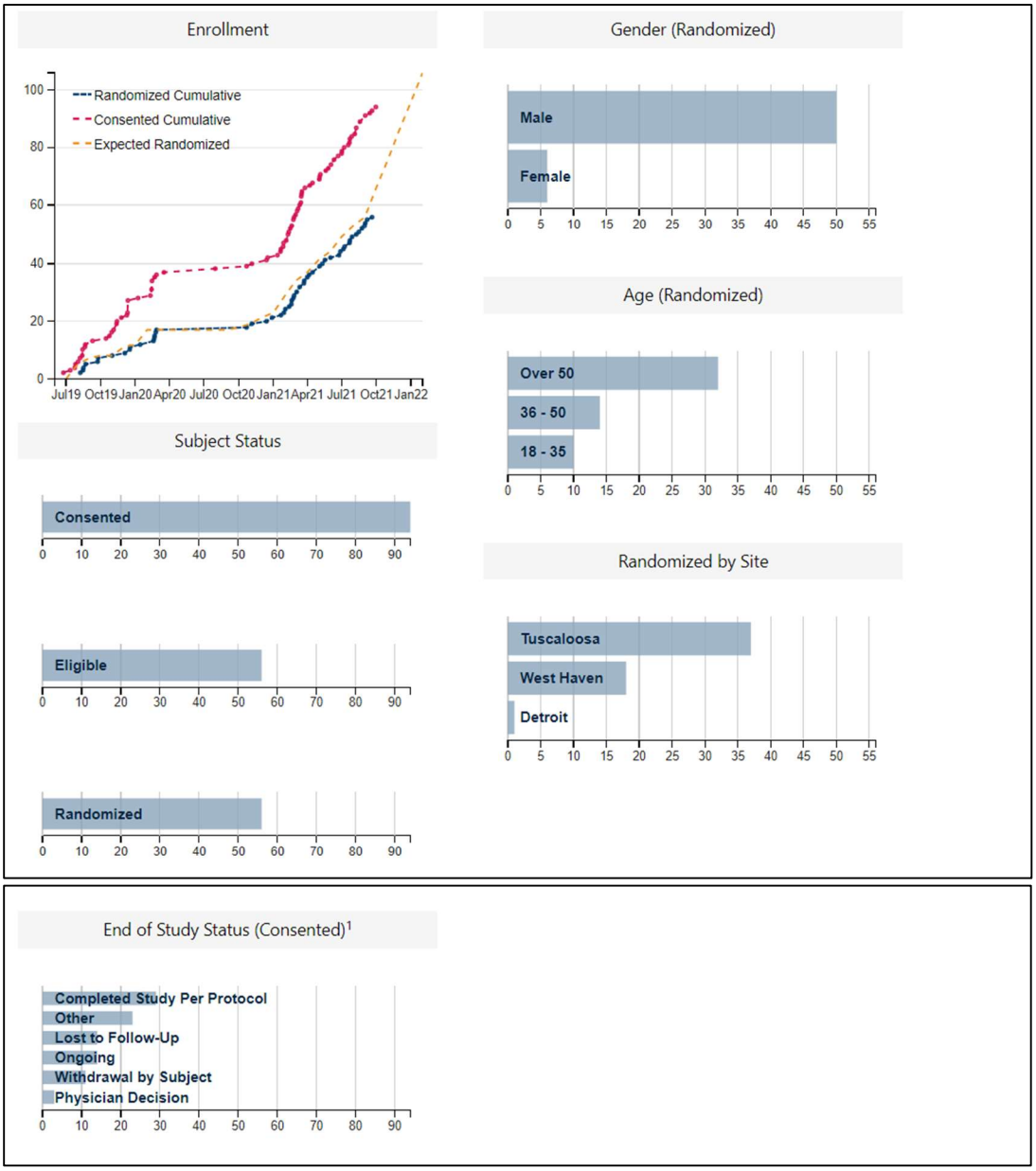

Figure 2: Study Dashboard. As shown in the study dashboard, as of 30-SEPT-2021,

- First subject enrolled 20-MAY-2019

- 94 consented across all sites
- 56 randomized (37 Tuscaloosa, 18 West Haven, 1 Detroit)
- 39 completed primary endpoint week 8 (27 Tuscaloosa, 11 West Haven, 1 Detroit)
- 32 completed end of study week 12, (22 Tuscaloosa, 9 West Haven, 1 Detroit)

Retention at week 8 is currently at 70% but should be higher at study closure given that some are still active at earlier weeks at the time of this snapshot.

Additional delays in the 3rd quarter FY21 were result of a supply issue with keeping Vivitrol and placebo in stock at the facilities (vendor problem and weather-related interference with shipments). This problem has been solved and to prevent this problem from occurring in the future, Alkermes is keeping a much larger stock on hand at each site (15 instead of 3 kits for drug and placebo) to meet the needs of surge in enrollment and refills on the active participants.

GOAL #3. Conduct the Physiological Assessments for Aims 2, 3, and 4.

Prior to COVID-19 pandemic, 17 participants had completed the physiological assessments. An amendment was approved to restart assessments on 31-AUG-2021. Psychophysiological assessments are optional to the participant, depending on their preference, considering amount of time and travel burden. Data for the physiological assessments is being consolidated on the PASA database and is being evaluated for quality.

3.4.c Training and professional development provided:
Dr. Norrholm visited Tuscaloosa and West Haven sites in JUL-2021 to do refresher training in preparation for restarting Psychophysiology assessments.

3.4.d Dissemination to communities of interest:
Dr. Davis presented on the pipeline for new medications for the treatment of PTSD on the virtual annual American Society of Clinical Psychopharmacology in MAY 2021, and this study was displayed in one slide.

There are no results to disseminate currently since data collection is still ongoing.

3.4.e Plans for next reporting period to accomplish goals and objectives:
Goal #1: Continue study operations at all sites.

The investigators will maintain operations at all sites and continue to monitor levels of supplies, study drugs, staffing, and environmental factors. Regulatory requirements will be closely adhered to, and approvals will be sought in advance so that compliance issues do not surface.

Vacancies at Tuscaloosa VA will be filled during 1st quarter FY22. All new staff members will be immediately trained using archival videos, live web-based training by RTI and Co-PIs, and hands-on training by local site investigators.

The budget will be closely monitored to ensure that site resources are stable and sufficient. The team has restructured the budget to maintain sites through JUN-2022.

Study supplies and drug expiration dates are closely monitored so that new supplies and study drugs can be ordered in advance. Tonix Pharmaceuticals extended the expiration date on the SL-Placebo to JUN-2022. Local pharmacies continue to purchase the buprenorphine. Alkermes continues to supply the active and placebo Vivitrol.

The Data Monitoring Committee continues to meet every fourth months.

GOAL #2: Continue randomization and maintain retention ≥70% at week 8.

The team would like to randomize 44 more participants in FY22 with enrollment ending 01-MAR-2022 and last patient to exit week 14 on 15-JUN-2022 and no-cost extension ending 30-JUN-2022. Over the next 6 months, the two sites will need to randomize 7.33 per month (3.33/month at each site beginning 01-OCT-2021).

Assertive recruitment activities will include:

- Daily outreach to clinicians
- WebEx internal in-services
- Chart reviews for clinic patients each week
- Press releases will be issued again
- Flyers and study brochures placed in clinics and community settings
- Mail letters to potential subjects whose names and addresses have been pulled from VA Corporate Data Warehouse (CDW)
- Advertise in the newspaper and on social media
- Ad placement on Tuscaloosa VA Facebook page and on AL.Com.
- Letters will be mailed to all veterans enrolled with past diagnosis of PTSD and AUD. A preliminary list of names from Central Alabama VA Healthcare System yielded 13,000 names which is being narrowed to a geographically focused area which makes it feasible for veterans to participate. Participants may be screened via telehealth and seen for in-person visits at the Tuscaloosa VA Medical Center community-based clinic in Selma, AL.

Historically, interest in treatment related research studies tends to rise around and after the holidays. This will hopefully coincide with decreasing cases of COVID-19 and continued uptake of the COVID-19 vaccine, which will aid in overall recruitment and enrollment.

GOAL #3. Conduct more Physiological Assessments for Aims 2, 3, and 4.

Amendment approved in AUG-2021 for Tuscaloosa and West Haven to restart of the psychophysiological assessments. Psychophysiology assessments are optional to the participant, depending on their preference, considering amount of time and travel burden. The team's goal is to encourage participants to take part in this aspect of the protocol and get approximately 25 more participants included in this part of the protocol.

The investigators will maintain operations at all sites and continue to monitor levels of supplies, study drugs, staffing, and environmental factors. Study supplies and drug expiration dates are closely monitored so that new supplies and study drugs can be ordered in advance. All new staff members will be immediately trained using archival videos, live web-based training by RTI and Co-PIs, and hands-on training by local site investigators. Regulatory requirements will be

closely adhered to, and approvals will be sought in advance so that compliance issues do not surface. The budget will be closely monitored to ensure that site resources are stable and sufficient.

4. Impact

4.0 PASA Core

The work, findings, and specific products of the projects sponsored through PASA are still in progress, but collaboration on manuscripts has provided quality data to push innovations forward. As the Core continues to finalize and publish additional manuscripts, the Consortium strengthens its impact. Another important impact during this reporting period has been with the PASA Consortium pharmaceutical company partners. These partners have favorably noted the Consortium's major accomplishments, innovations, and successes for identifying promising new medications for substance use disorders. The Core has refined the RFA and project award process to better identify viable projects and to make initial low-funded awards to allow for better determination of clinical trial needs for potential compounds. The Core continues to build the PASA template library as well as the website to allow for efficiency and consistency across studies. The Core has also established excellent working relationships with several VAMCs across the USA for conducting the PASA clinical studies. The Core has used knowledge across studies conducted within the PASA consortium, as well as knowledge of clinical trials conducted outside of the PASA consortium by the team of established collaborators, to help inform initial and continued funding decisions for compounds being studied within PASA.

4.1 AS140026-A2 Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol Use Disorder

The study is published and has now concluded.

Haile, C.N., Carper, B.A., Nolen, T.L. *et al.* The GABAB receptor positive allosteric modulator ASP8062 reduces operant alcohol self-administration in male and female Sprague Dawley rats. *Psychopharmacology* (2021). https://doi.org/10.1007/s00213-021-05881-0

4.2 AS140026-A3b PT150 (formerly ORG 34517) as a Potential Treatment for Alcohol Dependence – Alcohol Interaction Study

The study is published and has now concluded.

Morice, C., Baker, D.G., Patel, M.M. et al. A randomized trial of safety and pharmacodynamic interactions between a selective glucocorticoid receptor antagonist, PT150, and ethanol in healthy volunteers. Sci Rep 11, 9876 (2021). https://doi.org/10.1038/s41598-021-88609-6

4.3 AS140026-A3c Effects of Ethanol on the Pharmacokinetics of PT-150 (Formerly ORG34517)

The study is still in the stage of start-up, therefore there are no findings available to change practice. There have been no patents or technology transfers developed in this study.

4.4 AS140026-A5 Kappa Opioid Receptor Antagonism for the Treatment of Alcohol Use Disorder and Comorbid PTSD

The study is still ongoing so other than the benefit that participants have had by being in treatment, the study has had no external impact on treatment guidelines or drug development.

5. Changes/Problems

5.0 PASA Core

The main challenge in the past year has been impact of the COVID-19 pandemic on research. Overall, most of the pre-clinical studies did not experience drastic setbacks; however, there were some study delays and modifications to some pre-clinical study and clinical trial protocols/procedures due to the pandemic. To mitigate study barriers as much as possible, the PASA Core tracked each site's status and routinely assessed for impacted abilities at the site level. Though there were some delays, sites are now fully reopened and operational and have adapted to the constraints inflicted by COVID. Of important note is that regulatory approvals from FDA and DoD advisory boards and local IRB and VA R&D committees remain on track for successful resolution toward clinical projects since COVID-19 restrictions were lifted.

A change to note would be the addition of Dr. Nathan Vandergrift as the PASA Consortium co-PI as replacement for previous Co-PI, Dr. Rick Williams. Dr. Vandergrift is a statistician with more than 15 years of experience in collaborative research in diverse areas such as public health–related infectious disease research, translational medicine from bench science, vaccine development, infectious disease treatment, community-level intervention for substance use disorder, pharmaceutical trials for substance use disorder, and large-scale educational and child development. His areas of statistical expertise are structural equation modeling, nonlinear and linear mixed-effects modeling, generalized linear models, nonparametric statistics, missing data, and statistical matching. Dr. Vandergrift has a depth of experience applying for, receiving, and executing large multisite UM1 and P01 grants and contracts and R01-level grants. He has led statistical teams and been a part of large collaborative research groups spanning many sites, countries, and continents. These collaborations have resulted in publications in highly regarded peer-reviewed journals and make him well suited for the Co-PI position.

5.1 AS140026-A2 Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol Use Disorder

No changes or problems to note. The study is published and has now concluded.

5.2 AS140026-A3b PT150 (formerly ORG 34517) as a Potential Treatment for Alcohol Dependence – Alcohol Interaction Study

No changes or problems to note. The study is published and has now concluded.

5.3 AS140026-A3c Effects of Ethanol on the Pharmacokinetics of PT-150 (Formerly ORG34517)

The research team has modified the master protocol to open recruitment to non-veterans as a preemptive measure to combat low recruitment numbers. The amendment allowing non-veterans was approved by the local IRB on 17-DEC-2020.

The COVID-19 pandemic and resulting closures of institutions/organizations has delayed opening the study up for recruitment. The study team has revised the protocol to include COVID-19 precautions for the subjects and study staff.

The research team is also looking to acquire additional staff to cover the various in-patient periods. The limited number of skilled applicants has delayed the hiring process, as has the need for staff capable of performing phlebotomy procedures on all shifts given the large number of participant blood draws required. The research team is looking to employ pre-existing research staff members from other groups

to fulfill the personnel requirement for the study. The current research coordinator has also obtained certification in phlebotomy to provide some added support as needed.

5.4 AS140026-A5 Kappa Opioid Receptor Antagonism for the Treatment of Alcohol Use Disorder and Comorbid PTSD

The protocol was amended 09-AUG-2021 to Version 7 for all sites to restart psychophysiological assessment, change participant payment schedule to align with procedures, update prohibited medication list to reduce unnecessary barriers, clarify exclusion criteria (i.e., change in upper limit for liver enzymes), and close Detroit site for enrollment.

The MAR-2020 COVID-19 shutdown has caused the most substantial delay. After medical centers started to reopen in 2021 for in-person visits, COVID-19 safety protocols were implemented, and the administrative hold on research was lifted, the investigators have been able to resume recruitment in AUG/SEPT-2020 with COVID-19 protocols in place. However, the new surge in the COVID-19 delta variant has caused some hesitancy for full in-person clinical services.

The Detroit site was closed to recruitment on 30-JUN-21. Funds have been reallocated to the Tuscaloosa and West Haven site to support a no-cost extension (NCE). Protocol amendments will be made to extend the recruitment period. A modest subaward is in place for Dr. Norrholm to conduct the training on psychophysiological assessments and data analysis. Funds have been reallocated to extend the project to 31-MAY-2022, and the prior NCE with maintain sites through 30-JUN-2022. The NCE, executed 26-SEPT-2021, will allow for continued recruitment at the Tuscaloosa and West Haven site to meet recruitment goals missed due to COVID holds and Detroit site closure. RTI has an approved plan to roll the analytic work into PASA 2, which allows sites to extend enrollment to 01-MAR-2022 and end study participants by 15-JUN-2022.

COVID-19 required a change in safety protocols to protect the health of research staff and research participants. These measures were described in detail in the amended protocol and approved by local IRBs.

The COVID-19 safety plan includes:

- Vaccinations for employees
- Vaccinations for veterans
- Screening for COVID-19 risk before entering medical center
- Wear face mask
- Social distancing
- Limit occupancy in clinic
- Telehealth visits as often as possible
- Optional collection of psychophysiological data
- Allow subjects to record alcohol usage on preprinted calendars in advance
- Allow subjects to be mailed self-reports so these can be completed at home and bring to visits, thus limiting the amount of time in research offices.
- Limit office visits to those which require medication administration and/or lab work, as much as possible.
- Include new mailing letter that addresses COVID-19 concerns.

6. Products

6.0 PASA Core

Specific products that have resulted from these projects during the reporting period include conference papers and presentations and publications.

Presentations

Presentations are as noted above.

Publications

Publications are as noted above.

7. Participants and Other Collaborating Organizations

RTI International - Management Core

Nolen, Tracy	Principal Investigator	13%
Baldi, Marjorie	Financial/Subcontracts Mgr	11%
Arafat, Dana	Financial/Subcontracts Mgr	6%
Bradley, Lauren	Research Coordinator	9%
Crawford, Meg	Research Coordinator	9%
Fain, Katie	Research Coordinator	10%
Hirsch, Shawn	Statistician	22%
Jones, Alexis	Research Coordinator	5%
Kendrick, Amy	Research Coordinator	12%
LeGrow, Keith	Programmer/Analyst	7%
Nowak, Kayla	Statistician	12%
Roberts, Cheryl	Clinical Data Manager	11%
Smith, Emily	System Analyst	3%
Tang, Yan	Programmer/Analyst	4%
Turner, Eugene	Clinical Data Manager	11%
Vandergrift, Nathan	Co-Principal Investigator	6%
Bilbrey, Hudson	Website admin/developer	9%
Williams, Rick	Co-Principal Investigator	8%
Hudspeth, Julie	Financial Analyst	3%
Gatto, Gregory	Regulatory Affairs Lead	5%
Pickett, James	Programmer/Analyst	3%

Baylor College of Medicine - Management Core

Kosten, Thomas	Co-Principal Investigator	25%
Domingo, Coreen	Site Coordinator	75%

University of Houston

Assessing Pharmacotherapies in Animal Models of Post-Traumatic Stress Disorder and Alcohol use Disorder

Haile, Colin	Principal Investigator	10%
Kosten, Therese	Co-Principal Investigator	10%

Baylor College of Medicine

Effects of Ethanol on the Pharmacokinetics of PT-150 (Formerly ORG34517) (Study AS140026-A3c)

Verrico, Christopher	Principal Investigator	25%
Kosten, Thomas	Co-Principal Investigator	25% (no cost)
Vaughan, Adetola	Study Coordinator	50%

Veterans Medical Research Foundation

Effects of Ethanol on the Pharmacokinetics of PT-150 (Formerly ORG34517) (Study AS140026-A3c)

Baker, Dewleen	Principal Investigator	8%
Patel, Anjana	Project Manager	2%

Tuscaloosa Research & Education

Kappa Opioid Receptor Antagonist for the Treatment of Alcohol Use Disorder and Comorbid PTSD Planning Grant

Davis, Lori	Co-Principal Investigator	20%
Petrakis, Ismene	Co-Principal Investigator	20%
Norrholm, Seth	Co-Investigator	20%
Pilkinton, Patricia	Co-Investigator	10%
Brittney Washington-Ball	Study Coordinator	100%
Alexis Crawford	Study Coordinator	100%
Estes, Sandra	Project Manager, Primary Independent Assessor	2%
Kim McCal	Independent Assessor	5%
Newcomb, Jenelle	Primary Study Coordinator	90%
Serrita, Jane	Independent Assessor	14%
Lucienne Levy	Back-up Study Coordinator	34%
Riser, Manessa	Research Coordinator	1%
Woodford, Jessica	Independent Assessor	0%
Sharon Sloup	Research Nurse Practitioner	2%
Stephen Brackett	Local Site Investigator	1%
Palmissano, Alexandra	Independent Assessor	<5%
Ralevski, Elizabeth	Co-investigator	<5%
Yoon, Gihyun	Co-investigator	<5%

7.1. AS140026-A3c Effects of Ethanol on the Pharmacokinetics of PT-150 (Formerly ORG34517)

7.1.a. Has there been a change in the other active support of the PD/PIs or senior/key personnel since the last reporting period?

Dr. Christopher Verrico (PI): No change

Dr. Thomas Kosten (Co-PI): No change

Ms. Adetola Vaughan (Study Coordinator): No change

7.2. AS140026-A5 Kappa Opioid Receptor Antagonism for the Treatment of Alcohol Use Disorder and Comorbid PTSD

7.2.a. Has there been a change in the other active support of the PD/PIs or senior/key personnel since the last reporting period?

The Lead Coordinator (Brown) at the Tuscaloosa site resigned from her position as of 3-SEPT-2020. Two research coordinators (Crawford and Washington-Ball) were hired to cover the Tuscaloosa site and recruitment from the extended catchment areas including Birmingham, Montgomery, and Selma. Their start dates were 16-NOV-2020 and 17-NOV-2020. However, one of these coordinators (Crawford) resigned to take another VA position. Her last day was 24-SEPT-2021. The position is currently posted. The back-up coordinator also resigned to take another position and that position is being advertised to be filled as soon as possible. The past nurse project coordinator (Estes) is no longer employed but duties have been re-assigned.

Dr. Norrholm's effort was reduced due to site enrollment closure on 30-JUN-2021. Effort of the remaining site staff ended at that time. Dr. Norrholm will continue with the project to keep site research coordinators trained and proficient on the psychophysiological assessments, to answer their questions and solve barriers in logistics of conducting the psychophysiological assessments, to coordinate the upload of civilian trauma virtual environment within the psychophysiological assessment package, to receive raw data and finalize scoring of the psychophysiological assessments, to oversee data and scoring with RTI-PASA statisticians and programmers on the psychophysiological assessments, and to conduct the analysis in collaboration with RTI-PASA statisticians and programmers on the psychophysiological assessments.