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PRINCIPAL INVESTIGATOR: Dr. Tracy Nolen, DrPH

CONTRACTING ORGANIZATION: Research Triangle Institute, Research Triangle Park, NC

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Research Triangle Institute
3040 Cornwallis Road
Research Triangle Park, NC
27709

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14. ABSTRACT

The PASA objective is to identify promising potential treatments for ASUD particularly in the presence of other psychological disorders including PTSD. Of particular concern is opioid use disorder (OUD) in Veterans. Veterans with PTSD appear to be more susceptible to develop OUD, and the prevalence of this is increasing. Therefore, the PASA Core solicits, funds, and participates in the conduct and analysis of non-clinical basic science studies, preclinical animal research studies, and early-phase clinical trials of potential treatment compounds. The intention of these studies is to provide early-stage evidence that these compounds are safe and potentially effective in treating ASUD, particularly in the presence of PTSD and other psychological disorders.

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None listed.

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1. Introduction

The Pharmacotherapies for Alcohol and Substance Use Disorder Alliance (PASA) is funded by the Congressionally Directed Medical Research Programs (CDMRP) as part of its Alcohol and Substance Use Disorder Research Program (ASUDRP). The goal of the PASA is to fund research for developing new medications that can improve treatment outcomes for alcohol and substance use disorders (ASUD), especially as related to post-traumatic stress disorder (PTSD) and other psychological disorders. Research proposed can be for an alcohol use disorder (AUD), substance use disorder (SUD), or both an AUD and SUD.

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 AUD, 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 PASA.

PASA 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.

- ***Aim 1:*** *Discover: Test new chemical entities and repurpose existing medications in strictly pre-clinical and non-clinical models of ASUD with comorbid PTSD and other psychological disorders.*
- ***Aim 2:*** *Phase 1 First-in-Human Safety: Conduct clinical trials of potential medications that include assessment of medical safety and doses for potential efficacy in subjects with ASUD and comorbid PTSD and other psychological disorders.*
- ***Aim 3:*** *Phase 2 Efficacy: Conduct multiple site clinical trials to test preliminary efficacy and safety of potential medications or medication combinations in humans with ASUD and comorbid PTSD and other psychological disorders, and to also explore precision medicine tools for matching patients to these medications.*

2. Keywords

- alcohol and substance use disorder (ASUD)
- alcohol use disorder (AUD)
- substance use disorder (SUD)
- opiate use disorder (OUD)
- post-traumatic stress disorder (PTSD)
- request for applications (RFA)
- pharmacotherapy

3. Accomplishments

In addition to routine monitoring and supporting ongoing studies, our overarching accomplishments for the first year were:

- Expand PASA footprint, project portfolio and collaborating investigator network:

- RFA7 released 06/02/2023 for four different award types (Clinical Trial Planning, Pre-clinical, Non-clinical, and Existing Study Expansion Awards).
    - There were 48 letters of intent (LOI) submitted and 36 full RFA submissions.
    - After undergoing first peer review and then Programmatic Panel review and discussion, 5 submissions (1 expansion, 2 pre-clinical, and 2 planning awards) were selected for funding and contracting will begin next quarter.
    - 3 awards are with new institutions/investigators.
  - Additionally, the Effect of Sublingual formulation of Dexmedetomidine HCl (BXCL501) on ***Ethanol in Heavy Drinkers with PTSD – <u>Outpatient Study</u>*** was also approved for funding by the Programmatic Panel. This is the subsequent outpatient of the previously funded PASA II AS170014-A7: BXCL501-Alcohol interaction laboratory Study with Dr. Petrakis
- Expanding future clinical trial pipeline for PASA via:
  - Contract executed and protocol and clinical development planning underway and will be ready for funding evaluation by the Programmatic Panel in early 2023 for AS210006-A2/ Suvorexant Planning Award with Drs. Ray (UCLA) and Lane (UTHealth).
- Launched new PASA-funded studies via:
  - Launched new non-clinical research project (AS210006-A1/Leverage Electronic Medical Records/Dr. Wang). The research team's contract was executed and work launched late 2022. The research team launched all three study Aims, with 3 manuscripts in process based on the Aim 1 work.

3.0 PASA Activities

Activities under PASA III commenced in Year 1 with oversight from ongoing PASA I and II research activities.

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

The primary PASA objective is to efficiently manage and monitor studies that lead to accurate, quality data for publication and dissemination. This is achieved through PASA management responsibilities such as regularly scheduled check-ins, follow-ups, data accountability, statistical analysis, quality control and assurance, and other various oversight activities.

Consistent with the 3 Aims of this program as detailed in the Introduction, the overall focus of the PASA project is in (i) aiding 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 of objectives. PASA ensured close communication with all research sites and tracked status through shared internal documentation.

During Year 1, 2 projects from RFA6 cycle were funded out of PASA3 funding. Also, RFA7 was released to the public (planning award, pre-clinical, non-clinical, and expansion awards) on 06/02/2023 (coincided with investigator meeting). The Programmatic Panel (PP) reached consensus to fund an additional 6 projects under PASA3 (detailed below).

3.0.b Accomplishments under the goals include:

- Monitored and supported the 1 non-clinical and 1 clinical planning award funded out of RFA#6.

- Completed activities in support of RFA #7 including Programmatic Panel approval and funding of 2 planning awards, 2 pre-clinicals studies, 1 expansion award, and a clinical trial.

3.0.c Training and professional development provided:
The PASA data coordinating center (DCC) staff performing study related activities on PASA are responsible for complying with training requirements set forth by RTI and federally mandated regulations. All PASA DCC staff performing study related activities train on the PASA and RTI standard operating procedures (SOPs). Exceptions to this requirement are for staff who solely manage either the PASA website or manage the financial/subcontracting processes. Individual staff are responsible for providing clearly labeled documentation of relevant training files for PASA.

For study site staff, PASA monitors that personnel are adequately trained on all relevant study documents, as warranted per their study role, including but not limited to the study protocol, manual of procedures (MOP), electronic data capture system (EDC), and other applicable study materials.

3.0.d Dissemination to communities of interest:
PASA hosts a public and private website. The private side of the website is password protected and has role-based access for unaffiliated individuals, PASA-affiliated individuals, and funded researchers. An expertise directory, study specific templates, tools, dashboards, and trackers are accessed via the private side of the portal. The public side of the website allows dissemination of public information on PASA, including updates on completed research and information on funding opportunities.

PASA personnel disseminate study results and data through regulatory submissions to the FDA, study specific manuscripts, conference workshops and presentations, and other modes of public dissemination (e.g., the website).

3.0.e Plans for next reporting period to accomplish (goals and objectives):
Over the next reporting period, an ongoing focus will be providing support for PASA funded studies including launching the 6 new research projects approved for funding from the RFA#7 process. Under PASA3, we will also support the maintenance and upgrades of the web presences developed under PASA2, host the in-person 2024 Investigator meeting, and conduct another workshop panel (planned for RFA). We will also organized and conduct virtual working group meetings of investigators on keep topics of interest (e.g., appropriate animal disease models, recruitment and retention).

3.1 AS10006-A1 Leverage EMR to Identify Medications Repurposing for Treatment of ASUD with Comorbid PTSD / Dr. Wang
The objective of this project is to leverage electronic medical records (EMR) to identify medications for repurposing with respect to treatment of ASUD with comorbid PTSD. The scope involves applying machine learning, deep learning techniques and natural language processing techniques to predict the onset of ASUDs, identify drugs that increase or decrease risk and analyze how inclusion of multimodal information such as diagnosis, medication use, lab test results, social determinants of health, psychotherapy and research of domain criteria interact with these risk factors among PTSD patients. Ultimately, the project aims to inform interventions and optimize treatment for this high risk underserved population.

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

The major goal and objective were to identify potential medications for treating individuals with both alcohol and substance use disorders and comorbid post-traumatic stress disorder, a group that faces an increased risk of suicidal behaviors and deaths. The research team analyzed electronic medical records (EMR) of these patients, they aimed to find medications that may reduce the risk of adverse outcomes, including suicide related behaviors and depression. They utilized both structured and unstructured EMR data to extract multimodal information (i.e., diagnoses, medication use, lab test results, psychotherapy status, social determinants of health and research of domain criteria) to understand potential new medications for better outcomes (**Figure 1**).

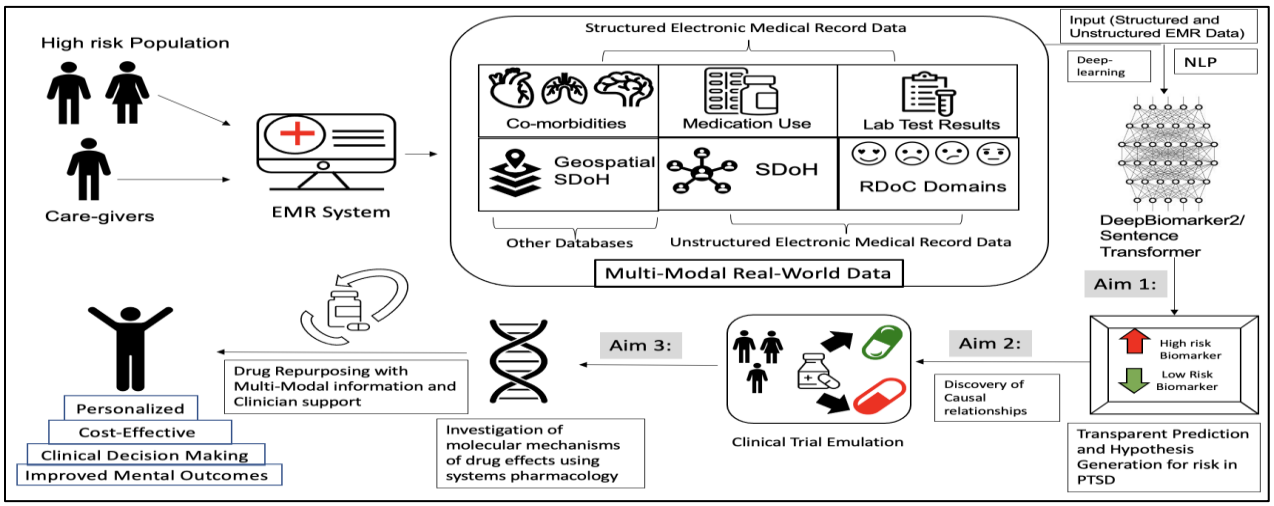

Figure 1. Overview of the EMR project.

3.1.b Accomplishments under the goals include:

The major accomplishments under *Aim 1* of this project include:

- Build/refine the research team's predictive deep learning models on predicting single outcome (i.e., ASUD risk) of 38.807 PTSD patients.
- Extracted new multimodal information (i.e., cognitive behavioral status and trauma focused psychotherapy status) from unstructured EMR using natural language processing techniques.
- Build/refine the research team's dictionary for identification of cognitive behavioral status and trauma focused psychotherapy status from unstructured EMR data (i.e. ,5.8 million clinical notes) with the help of subject matter expertise (including PASA team members).
- Used sentence transformer model to identify which patients have active cognitive behavioral status and trauma focused psychotherapy status and number of times they underwent cognitive behavioral and trauma focused psychotherapy in their entire disease trajectory to capture treatment bias.
- Generated a new deep learning model which leverages both deep learning and natural language processing techniques and uses multimodal information extracted both from structured and unstructured EMR data (i.e., diagnoses, medication use, lab test results, individual level social determinants of health, neighborhood level social determinants of health, cognitive behavioral status and trauma focused psychotherapy status) to predict the risk of developing ASUD in PTSD patients.

- Refined the research team's statistical analysis to remove bias caused by using deep learning models and extracted key features/factors that would be crucial for tailoring personalized treatments for these patients.
- Applied the research team's deep learning model to predict the risk of multiple developing adverse events (i.e., suicide related events [suicidal ideations, attempts and death], opioid use disorder, death) in PTSD+AUD patients.
- An organizational meeting with Drs. Wang, Davis, Kosten and their associates has been scheduled for next reporting period for starting parallel data analyses in the VA system to those that have been ongoing in the University of Pittsburgh hospital system for medication re-purposing. A meeting is also being coordinated with the OMICS group at RTI under Dr. Webb with Drs. Wang and Kosten.

These accomplishments produced the following results:

- A deep learning-based model DeepBiomarker2 (**Figure 2**) has been developed for the prediction of ASUD risk among PTSD patients with very good performance (**Table 1**). As shown in **Table 1**, Deep learning models: TLSTM and RETAIN algorithms implemented in DeepBiomarker2 all showed excellent performance on ASUD prediction, i.e., all yielded an AUC ≥0·90. The performance of deep learning (AUC above 0·93) was better than LR (0·85). The performance of models with SDoH are slightly better than those without SDoH.

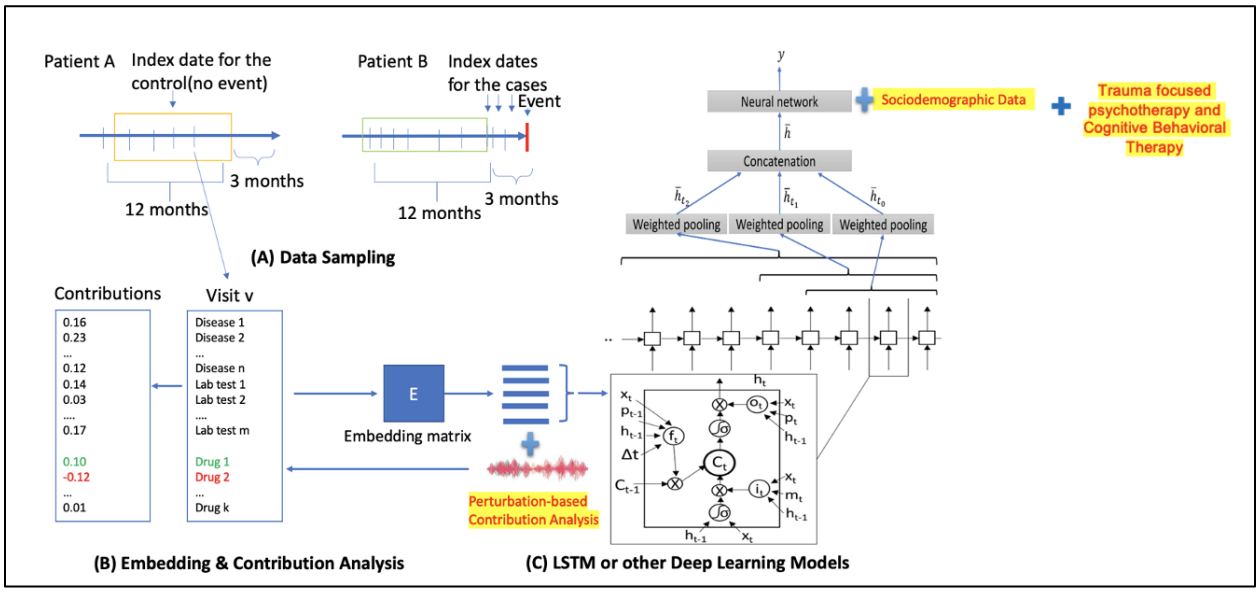

Figure 2. Overview of DeepBiomarker2. (A) Data sampling from electronic medical records: Patient A and B both pass the inclusion criteria and within the given time interval, Patient A has no event and Patient B has events and are considered as a control and a case, respectively. The research team extracts patient multimodal information (i.e., Diagnoses/Disease, Medication use/Drug and Lab-test results from their EMRs and use them as input in the research team's model, (B) Data embedding: The multimodal information is then converted into continuous vector spaces to build an embedding matrix and (C) Prediction by neural networks such as TLSTM and RETAIN as the basic prediction units. The research team then incorporates individual and neighborhood level SDoH information, trauma focused psychotherapy and cognitive behavioral status information in the team's neural networks for outcome prediction. The team's model provides us with a comprehensive list of multiple biomarkers and with the help of the perturbation-based contribution analysis they calculate the relative contribution and identify the most important features/biomarkers. LSTM: Long Short-Term Memory; Dx: diagnosis.

Table 1. The performance metrics of DeepBiomarker2 with different deep-learning and machine learning algorithms with and without SDoH features.

RETAIN(+SDOH)	1	2	3	4	5	average	std·s
Validation AUC	0·922	0·925	0·927	0·934	0·935	0·929	0·005
Test AUC	0·918	0·927	0·930	0·933	0·928	0·927	0·007
Test Precision	0·886	0·890	0·899	0·915	0·886	0·895	0·013
Test Recall	0·850	0·878	0·865	0·867	0·869	0·866	0·011
Test F1	0·868	0·884	0·882	0·890	0·877	0·880	0·009
RETAIN(-SDOH)	**1**	**2**	**3**	**4**	**5**	**average**	**std·s**
Validation AUC	0·926	0·921	0·933	0·933	0·922	0·927	0·006
Test AUC	0·923	0·918	0·916	0·932	0·927	0·923	0·006
Test Precision	0·898	0·878	0·857	0·888	0·866	0·878	0·017
Test Recall	0·867	0·870	0·872	0·882	0·881	0·874	0·007
Test F1	0·882	0·874	0·864	0·885	0·873	0·876	0·008
LR(+SDOH)	**1**	**2**	**3**	**4**	**5**	**average**	**std·s**
Validation AUC	0·875	0·872	0·871	0·876	0·868	0·872	0·003
Test AUC	0·849	0·841	0·845	0·854	0·844	0·847	0·005
Test Precision	0·758	0·702	0·714	0·746	0·723	0·729	0·023
Test Recall	0·825	0·872	0·858	0·849	0·838	0·848	0·018
Test F1	0·790	0·778	0·779	0·794	0·776	0·784	0·008
LR(-SDOH)	**1**	**2**	**3**	**4**	**5**	**average**	**std·s**
Validation AUC	0·869	0·868	0·869	0·851	0·868	0·865	0·008
Test AUC	0·846	0·843	0·843	0·828	0·841	0·840	0·007
Test Precision	0·704	0·706	0·692	0·752	0·773	0·725	0·035
Test Recall	0·897	0·889	0·904	0·776	0·787	0·851	0·063
Test F1	0·789	0·787	0·784	0·764	0·780	0·781	0·010
TLSTM(+SDOH)	**1**	**2**	**3**	**4**	**5**	**average**	**std·s**
Validation AUC	0·936	0·932	0·935	0·944	0·929	0·935	0·006
Test AUC	0·910	0·924	0·935	0·928	0·935	0·926	0·010
Test Precision	0·786	0·863	0·869	0·873	0·886	0·855	0·040
Test Recall	0·906	0·855	0·887	0·855	0·878	0·876	0·022
Test F1	0·842	0·859	0·878	0·864	0·882	0·865	0·016
TLSTM(-SDOH)	**1**	**2**	**3**	**4**	**5**	**average**	**std·s**
Validation AUC	0·931	0·939	0·937	0·937	0·941	0·937	0·004
Test AUC	0·919	0·925	0·925	0·923	0·931	0·924	0·005
Test Precision	0·826	0·869	0·869	0·836	0·882	0·857	0·024
Test Recall	0·902	0·878	0·859	0·888	0·859	0·877	0·019
Test F1	0·862	0·874	0·864	0·862	0·871	0·866	0·005

*AUC: area under curve; std: standard deviation, TLSTM: Time-Aware Long Short-Term Memory; RETAIN: Reverse Time AttentIoN model; LR: Logistic regression; std.s: Standard deviations of validation AUC, test AUC, test precision, test recall and test F1, respectively.

- Identified important indicators for the ASUD prediction by perturbation-based importance analysis (**Tables 2-4**). Table 2, Table 3, Table 4 and Table 5 enlist the top important abnormal lab tests, medication use, diagnosis and SDoH parameters, respectively. The top important indicators were ranked based on the highest number of cases and controls and the most significant p-values. The factors marked in red are indicators of increased risk and ones marked in green are indicators of decreased risk.

Table 2. Top important abnormal lab test results identified by perturbation-based contribution analysis for ASUD prediction. In Table 2, HGB with RC of 1.45, along with other abnormal lab tests with RC>1 are indicators of increased risk for ASUD.

Feature Name	Relative Contribution	Wilcoxon_p	FDR_Q
HGB	1·46	2·63E-34	8·75E-35
HCT	1·40	5·43E-29	1·36E-29
Glucose	1·32	9·64E-28	1·93E-28
RBC	1·28	4·99E-16	4·99E-17
WBC	1·32	6·02E-14	5·47E-15
CL	1·29	8·99E-14	7·49E-15
MCHC	1·34	9·79E-13	7·53E-14
MCH	1·31	4·18E-11	2·78E-12
Albumin	1·35	5·77E-11	3·61E-12
RDW	1·30	7·80E-11	4·59E-12
Total Protein	1·41	1·31E-09	6·57E-11
Protein-Urine	1·41	2·20E-09	1·00E-10
Leukocyte Esterase	1·36	9·21E-09	3·54E-10
ABS NEUTROPHILS	1·33	1·95E-08	6·95E-10
CO2	1·28	0·0001	2·87E-06
Urea Nitrogen	1·20	0·0001	2·87E-06
Ca	1·27	0·0003	5·77E-06

*Relative contribution value > 1: Risk and Relative contribution value; < 1: FDR_Q: false discovery rate adjusted Q value, p_wilcoxon: P values of Wilcoxon test. Hemoglobin (HGB), hematocrit (HCT), red cell distribution width (RDW), red blood cells (RBC), white blood cells (WBC), absolute (ABS) neutrophils, mean corpuscular hemoglobin (MCH),mean corpuscular hemoglobin concentration (MCHC), chloride (CL), carbon dioxide (CO2), and calcium (Ca).

Table 3. Top important medication uses results identified by perturbation-based contribution analysis for ASUD prediction. In Table 3, pain medications such as acetaminophen and oxycodone both have an RC of RC>1 which are categorized as indicators of increased risk for ASUD while medications such as clindamycin and enalapril have an RC<1 and are categorized as indicators of decreased risk for ASUD.

Feature Name	Relative Contribution	Wilcoxon_p	FDR_Q
Acetaminophen	1·60	3·67E-38	1·84E-38
Hydrocodone	1·42	1·38E-10	7·66E-12
Oxycodone	1·44	3·49E-10	1·84E-11
Diphenoxylate Atropine	0·30	4·07E-08	1·40E-09
Sodium sulf/Sod	0·45	2·52E-07	7·87E-09
Gabapentin	1·39	4·16E-07	1·26E-08
Enalapril	0·48	0·0001	2·84E-06
Moxifloxacin	0·31	0·0003	5·46E-06
Alprazolam	1·63	0·0019	2·89E-05
Symbicort	1·36	0·0228	0·0003
Clindamycin	0·59	0·0295	0·0003
Xarelto	0·39	0·0337	0·0004
Valacyclovir	0·53	0·0495	0·0005
Penicillin	0·65	0·0735	0·0007

*Relative contribution value > 1: Risk and Relative contribution value; < 1: FDR_Q: false discovery rate adjusted Q value, p_wilcoxon: P values of Wilcoxon test.

Table 4. Top important diagnosis results identified by perturbation-based contribution analysis for ASUD prediction. In Table 4, diagnosis such as routine lab examinations are categorized as protective factor for ASUD (RC=0.71) while other chronic pain is categorized as risk factor for ASUD (RC=1.17).

Feature Name	Relative Contribution	Wilcoxon_p	FDR_Q
Routine general medical examination at a health care facility	0·71	9·76E-25	1·63E-25
Esophageal reflux	1·25	1·40E-16	1·68E-17
Asthma, unspecified type, unspecified	1·34	1·51E-16	1·68E-17
Long-term (current) use of anticoagulants	1·24	4·82E-09	2·10E-10
Personal history of tobacco use	1·25	8·78E-09	3·51E-10
Anxiety state, unspecified	1·18	1·21E-08	4·49E-10
Lumbago	1·25	8·80E-07	2·45E-08
Personal history of other mental disorders	1·28	1·15E-06	3·10E-08
Depressive disorder, not elsewhere classified	1·21	4·54E-06	1·16E-07
Periumbilical pain	1·17	1·93E-05	4·48E-07
Fibromyalgia	1·19	0·0024	3·58E-05
Migraine without aura, with intractable migraine, so stated, without mention of status migrainosus	1·17	0·0146	0·0002
Osteoarthrosis, unspecified whether generalized or localized, site unspecified	1·26	0·0157	0·0002
Arthrodesis status	1·18	0·0192	0·0002
Body Mass Index, pediatric, greater than or equal to 95th percentile for age	0·86	0·0261	0·0003
Other chronic pain	1·17	0·0704	0·0007
Screening for malignant neoplasms of cervix	0·86	0·5997	0·0037

*Relative contribution value > 1: Risk and Relative contribution value; < 1: FDR_Q: false discovery rate adjusted Q value, p_wilcoxon: P values of Wilcoxon test.

- Identified SDoH and psychotherapy parameters for ASUD prediction(**Table 5**).

Table 5. Top important SDoH and psychotherapy parameters identified by averaging 10 repeats for ASUD prediction. In Table 5, cognitive behavioral therapy and trauma focused psychotherapy were found to be beneficial to reduce ASUD risk.

Name	Mean	sd	P	Impact on ASUD risk	Type of SDoH
Race (White)	0·120	0·02	2·60E-09	White patients have higher risk of ASUD	Individual
Trauma focused psychotherapy	-0·0812	0·016	1·49E-08	Individuals undergoing trauma focused psychotherapy have lesser risk of ASUD	Individual
Neighborhood socioeconomic status	-0·0943	0·033	3·27E-06	Neighborhoods with low socio-economic status has higher risk of ASUD	Neighborhood
Percentage of Non-Citizens	-0·116	0·04	3·43E-06	Non-US Citizens have a higher chance of ASUD risk	Neighborhood
Cognitive behavioral therapy	-0·0623	0·022	3·66E-06	Individuals undergoing cognitive behavioral therapy have lesser risk of ASUD	Individual
Percentage of Foreign born	-0·0901	0·033	5·08E-06	US born patients have higher risk of ASUD	Neighborhood
People of color index	-0·0778	0·03	9·88E-06	Black majority have higher risk of ASUD	Neighborhood
Limited English-speaking household	-0·106	0·042	1·00E-05	Households with limited English speaking capacity have higher risk of ASUD	Neighborhood
Racial segregation	-0·118	0·047	1·30E-05	High racially segregated zip codes have higher risk of ASUD	Neighborhood
Widowed partner who is a Male	-0·0781	0·032	1·41E-05	Widowed partner who is a male have lower risk of ASUD as opposed to widowed partner who is a female	Neighborhood
Household with transportation barriers	0·0870	0·04	3·82E-05	Households with no vehicles have higher risk of ASUD	Neighborhood
Gender	-0·0964	0·046	5·56E-05	Females have higher risk of ASUD	Individual
Age	-0·0828	0·043	0·0001	Younger patients have higher risk of ASUD	Individual
Household with same sex marriages	0·0652	0·039	0·0003	Households with same sex marriages have a higher chance of ASUD risk	Neighborhood
Aridity	-0·0487	0·03	0·0004	Low Humidity/lower vegetation/greenery have higher risk of ASUD	Neighborhood
Normalized difference vegetative index	-0·0581	0·043	0·0016	Low vegetation/greenery have higher risk of ASUD	Neighborhood
Gini index	-0·0216	0·019	0·0045	Zip codes with low gini index have higher risk of ASUD	Neighborhood
Household with Separated partners	0·0396	0·037	0·0063	Households with separated partners have higher risk of ASUD	Neighborhood
Income segregation	-0·0276	0·036	0·0309	Households with higher income segregation have higher risk of ASUD	Neighborhood

*SDoH: social determinants of health, sd: standard deviation, p: P values.

- Applied the abovementioned Deepbiomarker2.0 on the prediction of adverse events in PTSD+AUD patients and generate good results (**Table 6**).

Table 6. The performance of DeepBiomarker2 with and without SDoH features. Table 6 presents the performance results of the DeepBiomarker2 model, which incorporates deep learning algorithms such as LSTM and RETAIN, for predicting adverse events. The deep learning models demonstrate excellent performance, as indicated by AUC scores ≥0.90. This suggests that the deep learning models better capture more complex patterns and dependencies within the data, leading to improved predictive accuracy. Furthermore, the incorporation of SDoH factors, such as demographic and neighborhood-level information, provides additional valuable insight into multiple parameters impacting overall mental health. These findings reinforce the importance of leveraging advanced deep learning techniques and considering comprehensive contextual information in predictive modeling for improved clinical outcomes.

RETAIN(+SDOH)	**1**	**2**	**3**	**4**	**5**	**average**	**std.s**
Validation AUC	0.954	0.964	0.961	0.962	0.961	0.959	0.018
Test AUC	0.949	0.957	0.952	0.949	0.951	0.947	0.003
Test Precision	0.903	0.921	0.935	0.911	0.897	0.896	0.015
Test Recall	0.897	0.897	0.857	0.888	0.897	0.895	0.017
Test F1	0.9	0.909	0.894	0.899	0.897	0.895	0.006
RETAIN(-SDOH)	**1**	**2**	**3**	**4**	**5**	**average**	**std.s**
Validation AUC	0.954	0.955	0.964	0.963	0.966	0.960	0.006
Test AUC	0.95	0.95	0.95	0.948	0.947	0.949	0.001
Test Precision	0.866	0.887	0.899	0.893	0.903	0.890	0.015
Test Recall	0.922	0.909	0.899	0.892	0.891	0.903	0.013
Test F1	0.894	0.898	0.899	0.893	0.897	0.896	0.003
TLSTM(+SDOH)	**1**	**2**	**3**	**4**	**5**	**average**	**std.s**
Validation AUC	0.968	0.966	0.968	0.965	0.963	0.966	0.002
Test AUC	0.952	0.951	0.954	0.958	0.954	0.954	0.003
Test Precision	0.89	0.883	0.856	0.871	0.872	0.874	0.013
Test Recall	0.896	0.896	0.928	0.927	0.906	0.911	0.016
Test F1	0.893	0.89	0.891	0.899	0.889	0.892	0.004
TLSTM(-SDOH)	**1**	**2**	**3**	**4**	**5**	**average**	**std.s**
Validation AUC	0.962	0.971	0.969	0.967	0.963	0.966	0.004
Test AUC	0.948	0.947	0.956	0.959	0.951	0.952	0.005
Test Precision	0.832	0.853	0.885	0.927	0.898	0.879	0.037
Test Recall	0.922	0.902	0.902	0.888	0.889	0.901	0.014
Test F1	0.875	0.877	0.894	0.907	0.894	0.889	0.013

*AUC: area under curve; sd: standard deviation, T-LSTM: Tan Long Short-Term Memory; RETAIN: Reverse Time AttentIoN model; +SDOH/-SDOH includes/excludes social determinants of health factors.

- Identified important indicators for adverse events prediction by perturbation-based importance analysis (**Tables 7-9**). The results of this analysis are presented in Table 7, Table 8, Table 9, and Table 10, which highlights the top important abnormal lab tests, medication use, diagnoses and SDoH parameters, respectively.

Table 7. Top important abnormal lab test results identified by perturbation-based contribution analysis for adverse events prediction among PTSD+AUD patients. Table 7 demonstrates that all abnormal lab test results exhibits an RC>1, indicating that they are classified as risk factors for adverse events. The factors marked in red are indicators of increased risk and ones marked in green are indicators of decreased risk.

Feature Name	Relative Contribution	Wilcoxon_p	FDR_Q
Glucose	1.55	1.59E-168	1.59E-168
RBC	1.59	1.83E-129	9.16E-130
HGB	1.57	4.73E-127	1.58E-127
HCT	1.57	6.98E-125	1.74E-125
Albumin	1.79	8.25E-119	1.65E-119
CL	1.57	2.57E-87	4.28E-88
RDW	1.53	6.04E-81	7.55E-82
Sodium	1.59	9.66E-76	1.07E-76
Calcium	1.60	4.37E-75	4.37E-76
Urea Nitrogen	1.61	2.75E-74	2.29E-75
AST	1.57	4.00E-70	2.86E-71
MCHC	1.54	1.80E-66	1.20E-67
Platelets	1.70	7.30E-65	4.56E-66
CO2	1.67	1.75E-63	1.03E-64
Creatinine	1.68	3.47E-60	1.93E-61
MCH	1.51	1.17E-59	6.16E-61
Potassium	1.51	5.42E-58	2.71E-59
Lymphocytes	1.58	4.41E-54	2.10E-55
Total Protein	1.59	5.07E-54	2.30E-55
MCV	1.53	1.18E-52	4.91E-54
WBC	1.47	1.28E-52	5.12E-54

* Hemoglobin (HGB), hematocrit (HCT), chloride (CL), red cell distribution width (RDW), sodium (NA), calcium (CA), aspartate aminotransferase (AST), mean corpuscular hemoglobin concentration (MCHC), carbon dioxide (co2), mean corpuscular hemoglobin (MCH), potassium (K), and mean corpuscular volume (MCV). FDR_Q: false discovery rate adjusted Q value; Wilcoxon_p: P values with Wilcoxon test.

Table 8. Top important medications identified by perturbation-based contribution analysis in predicting adverse events among PTSD+AUD patients. As shown in Table 8, medications such as omeprazole, gabapentin, albuterol, ibuprofen hydrocodone and oxycodone have an RC>1, signifying their association with increased risk for adverse events. Other hand, medications such as piroxicam, vilazodone, dronabinol, tenofovir, suvorexant, empagliflozin, famciclovir, veramyst, amantadine, sulfasalazine, and lamivudine have an RC<1, indicating that they are categorized as protective factors against adverse events.

Feature Name	Relative Contribution	Wilcoxon_p	FDR_Q
Hydrocodone	1.55	4.45E-34	1.14E-35
Piroxicam	0.317	4.37E-16	4.50E-18
Vilazodone	0.190	9.97E-11	7.07E-13
Omeprazole	1.40	1.92E-10	1.29E-12
Oxycodone	1.33	1.01E-09	6.18E-12
Ibuprofen	1.40	6.14E-09	3.43E-11
Lamivudine	0.230	7.71E-09	4.24E-11
Albuterol	1.26	1.14E-07	5.40E-10
Gabapentin	1.23	2.13E-07	9.75E-10
Dronabinol	0.355	6.54E-06	2.32E-08
Tenofovir	0.481	0.00631	1.26E-05
Suvorexant	0.227	0.0115	2.18E-05
Empagliflozin	0.421	0.0454	7.73E-05
Famciclovir	0.309	0.0628	0.000104
Veramyst	0.426	0.105	0.000167
Amantadine	0.175	1	0.0133
Sulfasalazine	0.508	1	0.0115

*Relative contribution value > 1: Risk and Relative contribution value < 1: Protective; FDR_Q: false discovery rate adjusted Q value; Wilcoxon_p: P values with Wilcoxon test.

Table 9 (next page). Top important diagnoses results identified by perturbation-based contribution analysis for adverse events prediction among PTSD+AUD patients. In Table 9, diagnoses pertaining to pain, neuroinflammation and home accidents were risk factors for adverse events. These findings provide valuable insights into the potential impact of specific lab test results and medication use on the prediction of adverse events in PTSD+AUD patients. The identification of risk and protective factors can inform healthcare professionals in designing more targeted interventions and treatment plans to mitigate the occurrence of adverse events among PTSD+AUD patients.

Feature Name	Relative Contribution	Wilcoxon_p	FDR_Q
Tobacco use disorder	1.47	2.45E-86	3.49E-87
Esophageal reflux	1.48	7.45E-73	5.73E-74
Asthma, unspecified type, unspecified	1.52	5.77E-44	2.06E-45
Other, mixed, or unspecified drug abuse, unspecified	1.85	5.05E-41	1.58E-42
Personal history of tobacco use	1.47	5.36E-37	1.53E-38
Hypopotassemia	1.56	1.11E-32	2.77E-34
Suicidal ideation	1.65	6.80E-32	1.66E-33
Long-term (current) use of steroids	1.48	1.43E-29	3.25E-31
Home accidents	1.59	1.36E-27	2.96E-29
Abdominal pain, unspecified site	1.49	1.46E-27	3.11E-29
Obesity, unspecified	1.61	5.57E-26	1.01E-27
Unspecified sleep apnea	1.57	1.10E-24	1.77E-26
Lumbago	1.44	1.34E-21	1.91E-23
Personal history of colonic polyps	1.39	7.11E-21	1.00E-22
Other chronic pain	1.40	5.21E-18	6.28E-20
Epilepsy, unspecified, without mention of intractable epilepsy	1.44	7.46E-16	7.54E-18
Myalgia and myositis, unspecified	1.41	4.31E-15	4.06E-17
Other specified pre-operative examination	1.42	5.73E-14	4.98E-16
Anxiety state, unspecified	1.20	3.13E-09	1.84E-11
Other and unspecified hyperlipidemia	1.31	1.68E-08	8.84E-11
Pain in joint, forearm	1.33	4.32E-07	1.89E-09
Bipolar I disorder, most recent episode (or current) manic, unspecified	1.23	9.34E-05	2.63E-07
Inappropriate diet and eating habits	1.35	9.49E-05	2.67E-07

*Relative contribution value > 1: Risk and Relative contribution value < 1: Protective; FDR_Q: false discovery rate adjusted Q value; Wilcoxon_p: P values with Wilcoxon test.

- Identified SDoH parameters for adverse events risk prediction (**Table 10**).

Table 10. Top important SDoH identified for adverse events risk prediction

Name	Mean	sd	P	Impact on ASUD risk	Type of SDoH
Gender	-0.057	0.027	4.67E-05	Females have a higher risk of adverse events	Individual level SDOH
Park proximity	-0.050	0.030	3.48E-04	Neighborhoods with a low number of parks have a higher risk of adverse events	Neighborhood level SDOH
Percentage of Households with limited English speaking capacity	-0.058	0.036	4.31E-04	Households with high English speaking capacity have a higher risk of adverse events	Neighborhood level SDOH
Gini index	-0.059	0.037	5.25E-04	Neighborhoods with low Gini index have a higher risk of adverse events	Individual level SDOH
Percentage of Households with only English speaking individuals	0.032	0.021	7.54E-04	Households with individuals only speaking English and no other language are at a higher risk of adverse events	Neighborhood level SDOH
Percentage of foreign born	-0.043	0.035	0.0032	US-born patients have higher risk of adverse events	Neighborhood level SDOH
Health literacy status	-0.052	0.044	0.0039	Households with less health literacy have higher risk of adverse events	Neighborhood level SDOH
Household with no vehicles	-0.031	0.030	0.0084	Households with no vehicles have higher risk of adverse events	Neighborhood level SDOH
Income segregation	-0.033	0.036	0.0150	Households with higher income segregation have higher risk of adverse events	Neighborhood level SDOH
Race	0.017	0.020	0.0201	White patients have higher risk of adverse events	Individual level SDOH
Percentage of Non-Citizens	-0.021	0.031	0.0504	US Citizens have a higher chance of adverse events risk	Individual level SDOH
Neighborhood socio-economic status	-0.027	0.040	0.0535	Neighborhoods with low socio-economic status has higher risk of adverse events	Neighborhood level SDOH
Aridity index	-0.025	0.038	0.0541	Low Humidity/lower vegetation/greenery have higher risk of adverse events	Neighborhood level SDOH

*CI: confidence interval, SD: standard deviation

3.1.c Training and professional development provided:
The project provided numerous opportunities for training and professional development for PI and especially PI's graduate students. The research team participated in several workshops and courses focused on existing health disparities in alcohol and substance use disorder patients, application of artificial intelligence to advance healthcare and importance of personalized pharmacotherapy for military and veterans organized by University of Pittsburgh and MHSRS which significantly enhanced the research team's expertise to handle data and apply novel healthcare data strategies for broader applications. Additionally, PI Wang had the privilege of working closely with experienced scientists: Dr. Thomas Kosten, M Daniel Brannock and other PASA team members who provided valuable guidance and insights that were critical to the project. Moreover, the PASA annual meeting and MHSRS conference, the team attended expanded their professional network and helped them collaborate with other scientists who are established in this field.

3.1.d Dissemination to communities of interest:
The research team presented their findings at the PASA annual investigator meeting and the MHSRS Symposium. The team will publish their findings in journals soon.

> *Wang, et al., Incorporating Novel Deep Learning Models and Multiple Social Determinants of Health Parameters to Predict Alcohol and Substance Use Disorder Risk in Post-Traumatic Stress Disorder Patients Using Electronic Medical Records. Poster presented at: MHSRS Symposium; August 2023. Kissimmee, Fl.*

3.1.e Plans for next reporting period to accomplish (goals and objectives):
In Aim 1, the research team employed deep learning algorithms, natural language processing and statistical tools to analyze EMR data to understand potential new medications for better outcomes. While these results are not causal, in the next reporting period their major goal is to use clinical trial emulation (Aim 2) and systems pharmacology approaches (Aim 3) to understand causal relationships and provide molecular mechanisms that back these treatment options.

3.2 AS10006-A2 Development of Suvorexant for the Treatment of AUD and PTSD (Planning Award) / Drs. Ray and Lane
This project, and the clinical development plan supplements the protocol "A double-blind, randomized, Phase II study to compare the effectiveness of 20 mg oral suvorexant versus placebo (1:1) in participants with co-occurring Alcohol Use Disorder and co-occurring Posttraumatic Stress Disorder," by Drs. Lara Ray and Scott Lane (Co-PIs) for PASA funding consideration. The aim of the proposed clinical trial is to determine if suvorexant (SUV), a dual orexin antagonist that is FDA-approved for the treatment of insomnia, is effective at improving sleep metrics as well as reducing alcohol craving, alcohol use, and PTSD symptoms in individuals with co-occurring sleep disruption, alcohol use disorder (AUD), and Posttraumatic Stress Disorder (PTSD). The research team proposes a randomized, double-blind, placebo-controlled study of SUV. A total of 75 men and women veteran and non-veterans aged 21 to 65 with current AUD, PTSD and significant sleep disruption that are reporting motivation to address their drinking and PTSD symptoms. Eligible patients will be randomly assigned to receive 10mg to 20mg of SUV or matched placebo.

The proposed study specifically aims to assess the initial efficacy of suvorexant (10mg, 20mg) in improving sleep metrics. The secondary objectives of this study are: (1) to assess the effect of suvorexant (10mg, 20mg) on cue-induced alcohol craving by measuring the change in score from

Baseline to Day 14; (2) to evaluate the effect of suvorexant (10mg, 20mg) on drinking outcomes by calculating number of days abstinent, percent total days abstinent, and mean number of drinks per day (measured by Timeline Follow-back) during the 13-day quit attempt; and (3) to assess the initial efficacy of suvorexant (10mg, 20mg) in reducing PTSD symptoms by measuring the change from Baseline to Day 14 in the CAPS-5 and PCL-5.

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

- December 2022:
  - Completed revised budget for final PASA admin approval.
  - Finalized joint UTHealth-UCLA research proposal.
  - Finalized initial joint UTHealth-UCLA CDP document.
- February through March 2023: Held first 3 coordinated kick-off meetings (02/13; 03/13, 03/27) with UTHealth + UCLA teams and PASA leadership; set list of goals/action items for completion during planning award phase. Completed first working draft of CDP. Continued developing protocol.
- On 05/01/2023, the research team coordinated with Dr. Bailey and Dr. Ferzinger from Merck team (pharma collaborators) on regular meeting schedule. Solicited input from Merck team on CDP and protocol.
- On 06/02/2023, Dr. Ray (PI) presented working CDP at PASA Investigators Meeting.
- On 07/01/2023, the research team verified need for Merck MISP submission to obtain suvorexant and matching placebo from Merck. Completed and submitted MISP for 07/01/2023 deadline.
- On 08/15/2023, the research team coordinated Pre-IND meeting with Merck, established cross-reference for IND, if needed.
- On 08/31/2023, the research team established guidance on IND from PASA and Merck leadership. Additionally, they completed final revisions, updates, and received approval on Merck MISP for study medication.

3.2.b Accomplishments under the goals include:

All project planning milestones have been accomplished to date. The research team is still waiting for the FDA IND determination. Research project has not been initiated.

3.2.c Training and professional development provided:

Not applicable as this is a planning award.

3.2.d Dissemination to communities of interest:

Dr. Ray presented the proposed study methodology and progress at PASA investigator meeting. While the study remains under development currently, it may produce a medication which improves the treatment of PTSD/AUD for US Veterans.

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

- Finalize and submit IRB protocols for each institution following DSMB and Programmatic Panel review and feedback.
- Obtain DSMB and Programmatic Panel approval.
- Respond to FDA decision on IND. Submit full IND application if requested, and work with Merck team to cross reference Merck IND in the application process.
- Finalize budgets and get respective institutional approval/contract agreements in the event of approval from DSMB and programmatic panel.

4. Impact

4.0 PASA Management

Results Dissemination:

The work, findings, and specific products of the projects sponsored through PASA are ongoing, but collaboration on manuscripts and presentations has provided quality data to push innovations forward. As the PASA DCC and study leaders continue to finalize and publish additional manuscripts, this strengthens PASA's impact.

Pharmaceutical Partners:

Another important impact during this reporting period has been with PASA's pharmaceutical company partners. One new pharmaceutical company has partnered with PASA: Merck & Co., INC. This partner has favorably noted PASA's major accomplishments, innovations, and successes for identifying promising new medications for alcohol and substance use disorders.

Future Projects:

PASA 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.

Leveraging PASA Output:

Under PAS3A continues to build upon their existing template library as well as use the PASA website to allow for efficiency and consistency across studies. PASA has also established excellent working relationships with several VAMCs across the USA for conducting PASA clinical studies. PASA has used knowledge across studies conducted within the PASA, as well as knowledge of clinical trials conducted outside of the PASA with the PASA established collaborators, to help inform initial and continued funding decisions for compounds being studied within PASA. To further expand on PASA's ability to select novel compounds efficiently and effectively, PASA3 included funding of the AS10006-A1 EHR study to supplement the catalog of promising compounds (started under the PASA2 In silico project) that can then be incorporated into clinical or pre-clinical pursuits based on their novelty and fit in the regulatory pathway. Taking this additional step before implementing trials will help identify innovative therapies, ensure resources are utilized efficiently, and achieve the goal of expediting the translation from bench to bedside.

4.1 AS10006-A1 Leverage EMR to Identify Medications Repurposing for Treatment of ASUD with Comorbid PTSD

The impact of the EMR project during this reporting period has been significant. Here are the distinctive contributions and major accomplishments:

- Advancements in the field of leveraging EMR data for personalized pharmacotherapies for PTSD-ASUD by pioneering the identification of biomarkers that exert a dual influence on PTSD and ASUD, profoundly impacting their respective outcomes. The research team has achieved this through inclusion of multimodal real-world data, application of deep learning, machine learning and natural language processing and refining statistical tools. Since, mental health disparities is a critical challenge in high risk underserved populations, their multifaceted approach can help provide evidence-based treatments.
- Influence on data driven decision making by fostering collaboration between pharmacy, psychiatry, statistics and epidemiology. This synergy has resulted in better perspectives on drug repurposing and novel hypothesis generation obtained from their results. Inclusion of multi-

modal real-world data (i.e. different types of diagnosis, medication, lab tests, SDoH, RDoC, and psychotherapy) may offer significant advantages to both practitioners and researchers when it comes to tailoring these high risk patients. The benefits include holistic patient assessment, personalized treatment, early interventions, improved mental health outcomes, reduced health disparities and provide research insights.

- Innovations in technology, particularly in pharmaco-analytics. These innovations have the potential for a comprehensive understanding of the patient's health status. With a more complete picture of the patient's condition, their goal is to aid practitioners in developing personalized treatment plans that address the specific needs and challenges of each high-risk individual.

4.2 AS10006-A2 Development of Suvorexant for the Treatment of AUD and PTSD (Planning Award)
This project is a planning award to develop a clinical trial protocol, therefore, nothing to report.

5. Changes/Problems

5.0 PASA Management
The co-PI for this contract was changed from Dr. Nathan Vandergrift to Dr. Ryan Whitworth.

PASA continues to actively track each project's status and will assess any changes or problems that may arise to ensure projects remain on track.

5.1 AS10006-A1 Leverage EMR to Identify Medications Repurposing for Treatment of ASUD with Comorbid PTSD
No significant problems or issues.

5.2 AS10006-A2 Development of Suvorexant for the Treatment of AUD and PTSD (Planning Award)
The research project has not yet been initiated. However, in reaching the milestones pertaining to the project planning award, no significant changes/problems were encountered. Thus far, all milestones have been reached within anticipated target dates.

6. Products

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

Presentations

Presentations are as noted below.

Publications

Publications are as noted below.

6.1 AS10006-A1 Leverage EMR to Identify Medications Repurposing for Treatment of ASUD with Comorbid PTSD
The study team submitted two Manuscripts. **Submitted Manuscript #1** from the results obtained in Aim 1 work to Nature Mental Health and is under review.

DeepBiomarker2: Prediction of alcohol and substance use disorder risk in post-traumatic stress disorder patients using electronic medical records and multiple social determinants of health parameters.

Submitted Manuscript #2 also from the results obtained in Aim 1 work to Nature Mental Health and is under review.

Prediction of adverse events risk in patients with comorbid post-traumatic stress disorder and alcohol use disorder using electronic medical records by deep learning models.

The study team presented a Poster Presentation at the 2023 MHSRS Conference based on the results obtained in Aim 1.

Incorporating Novel Deep Learning Models and Multiple Social Determinants of Health Parameters to Predict Alcohol and Substance Use Disorder Risk in Post-Traumatic Stress Disorder Patients Using Electronic Medical Records.

Oshin Miranda**,** the team's graduate student, won two University of Pittsburgh annual awards:

- 2023 Health Disparities and Social Justice Poster Competition
- 2023 3-Minute thesis competition

6.2 AS10006-A2 Development of Suvorexant for the Treatment of AUD and PTSD (Planning Award)
The research team presented at the PASA Annual Investigator meeting.

Annual Meeting of PASA Investigators, Miami, Florida. "A double-blind, randomized, Phase II study to compare the effectiveness of 20mg oral suvorexant versus placebo (1:1) in participants with co-occurring Alcohol Use Disorder and Posttraumatic Stress Disorder," June 2023.

7. Participants and Other Collaborating Organizations

PASA DCC and Management (out of RTI International)

Nolen, Tracy	Principal Investigator	0%
Whitworth, Ryan	Co-Principal Investigator	3%
Kendrick, Amy	Lead Project Manager	3%
Vandergrift, Nathan	Statistician	0%
Beverly, Jennifer	Research Coordinator	1%
Brannock, Daniel	Senior Data Scientist	2%
Hirsch, Shawn	Statistician	1%
Hudspeth, Julie	Financial Analyst	1%
Okam, Ukoha	Financial Analyst	1%
Shafiei, Lyndsey	Research Coordinator	1%
Williams, Alexis	Research Coordinator	7%

Baylor College of Medicine (PASA Management)

Kosten, Thomas	PI/PD	25%
Domingo, Coreen	Key Personnel	75%

University of Pittsburgh

Leverage EMR to Identify Medications Repurposing for Treatment of ASUD with Comorbid PTSD

Wang, LiRong	Principal Investigator	20%
Ryan, Neal David	Co-Investigator	10%
Kirisci, Levent	Co-Investigator	10%
Miranda, Oshin	Graduate Student	100%

University of California at Los Angeles

Development of Suvorexant for the Treatment of AUD and PTSD

Ray, Lara	Principal Investigator	3.75%
Nieto, Steven	Co-Investigator	15%
Mooney, Larissa	Co-Investigator	2%
Jenkins, Jessica	Quality Assurance Manager	25%

UTHealth-Houston

Development of Suvorexant for the Treatment of AUD and PTSD

Lane, Scott	Principal Investigator	25%
Schmitz, Joy	Co-Investigator	5%
Acierno, Ronald	Co-Investigator	5%
Yoon, Jin	Co-Investigator	5%
Vincent, Jessica	Quality Assurance Manager	20%

7.1 AS10006-A1 Leverage EMR to Identify Medications Repurposing for Treatment of ASUD with Comorbid PTSD

7.1.a. Individuals who have worked on the project include:

LiRong Wang, PhD (PI): Responsible for all project activates conducted
Neal David Ryan, MD (Co-Investigator): Oversight and medical input into project activities.
Oshin Miranda, MS (Graduate Student): Carried out modeling activities under direction of investigators, including schematics of modeling and drafts of manuscripts and presentation slides.

7.2 AS10006-A2 Development of Suvorexant for the Treatment of AUD and PTSD (Planning Award)

7.2.a. Individuals who have worked on the project include:

At the UT Health Sciences Center:

Scott D. Lane, Ph.D. (PI): Responsible for all trial activates.
Joy M. Schmitz, Ph.D (Investigator): Input into project activities.
Ron Acierno, Ph.D. (Investigator): Input into project activities.
Jin H. Yoon, Ph.D. (Investigator): Input into project activities.
Deborah Little, Ph.D. (Investigator): Input into project activities.
Jessica Vincent, BS (QA manager): Responsible for managing day-to-day conduct of the study

At the University of California – Los Angeles:

Lara Ray, Ph.D. (PI): Responsible for all trial activates
Larissa Mooney, M.D. (Investigator): Input into project activities.
Steven Nieto, Ph.D. (Investigator): Input into project activities.
Jessica Jenkins, M.A. (QA manager): Responsible for managing day-to-day conduct of the study

7.2.b. Other organizations that have been involved as partners:

Merck & Co., INC., has joined as a research partner in the capacity that they will supply the medication (suvorexant) via a funded award through their Merck Investigator Studies Program (MISP).