AWARD NUMBER: W81XWH-14-1-0060

TITLE: Preventing Risky Drinking in Veterans Treated with Prescription Opioids

PRINCIPAL INVESTIGATOR: James R. McKay, Ph.D.

CONTRACTING ORGANIZATION: Trustees of the University of Pennsylvania, Philadelphia, PA

REPORT DATE: December 2020

TYPE OF REPORT: Final Report

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
December 2020	Final	01Apr2014-30Sep2020

4. TITLE AND SUBTITLE

Preventing Risky Drinking in Veterans Treated with Prescription Opioids

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-14-1-0060

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

James R. McKay, Ph.D.

E-Mail: jimrache@pennmedicine.upenn.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

AND ADDRESS(ES)

Trustees of the University of
Pennsylvania
3451 Walnut Street, 5th Floor
Philadelphia, PA 19104-6205

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

We will test an integrated prevention intervention, designed to reduce rates of risky drinking in veterans receiving prescription opioids for chronic pain. Veterans on prescription opioids who screen positive for risky alcohol use will be randomized to receive an adaptive integrated prevention intervention (IPI) or to standard care (SC). Veterans in the IPI condition who reduce alcohol use to non-hazardous levels during this one-month period continue in a monitoring track, consisting of tailored text messages and brief monthly telephone contacts. Veterans who continue to drink at risky levels are placed in a track that provides tailored text messages and more frequent telephone calls. All participants will be followed for 18 months. The primary outcome at each follow-up point will be measure of risky drinking. Secondary outcomes will include frequency of heavy drinking, biological measures of alcohol use and other drug use, opioid overdoses, and ratings of depression and pain. Repeated measures analyses will compare the IPI and SC conditions on primary and secondary outcomes assessed across an 18-month follow-up. Analyses will also test hypothesized moderation and mediation effects.

15. SUBJECT TERMS
None listed.

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	26	**19b. TELEPHONE NUMBER** *(include area code)*

TABLE OF CONTENTS

1. Introduction

Veterans who are taking prescription opioids for chronic pain and are engaging in risky drinking are at heightened risk for drug interactions, including overdose and other negative effects, particularly if they are also using benzodiazepines. In this application, we propose to test an adaptive prevention intervention, designed to reduce rates of risky drinking in veterans receiving prescription opioids to treat their chronic pain. This adaptive, patient-centered intervention provides clinical assessment, brief intervention, monitoring, and extended prevention services delivered through a combination of clinical visits, telephone calls, and text messages. We will conduct a study in which returning OEF/OIF individuals and other veterans receiving medical care at the Philadelphia VAMC, Pittsburgh VA, and the University of Pennsylvania (Original projected N=300; current goal N=150 who are on daily doses of prescription opioids and screen positive for risky alcohol use will be randomized to receive 12 months of an adaptive prevention intervention (API) or to standard care (SC), which consists of a Brief Intervention (BI) only. For veterans randomized to the API condition, a BI is first provided and the effects are monitored for one month. Veterans who reduce alcohol use to non-hazardous levels during this one-month period continue in a monitoring track, consisting of tailored text messages and brief monthly telephone contacts. Veterans who continue to drink at risky levels are instead placed in a track that provides tailored text messages and more frequent telephone calls. These calls provide monitoring and further prevention/BI services to help the veteran reduce alcohol use to non-hazardous levels. Key components of these services are motivational enhancement and development of more effective ways to cope with stress and other triggers for risky alcohol use. Veterans in the API condition who are initially placed in the monitoring track but whose drinking increases again during the 12 month intervention are transferred to the more intensive prevention track, until their alcohol use has again decreased. Additionally, Veterans who do not admit to drinking are placed in a monitoring track and if they admit to drinking, they are then placed into the treatment arm in which they were randomized to. API is hypothesized to produce better alcohol and other drug use outcomes than SC over an 18-month follow-up.

2. Key words

veterans, opioid medication, pain treatment, risky drinking, prevention, brief intervention, monitoring, adaptive interventions, benzodiazepines, overdose, follow-up

3. Accomplishments

Major Goals of the Project

The goal of the proposed study is to test an adaptive prevention approach designed for returning OEF/OIF individuals and other veterans who are engaging in risky drinking while being treated with prescription opioids for chronic pain. We propose to conduct a study in which returning OEF/OIF individuals and other veterans receiving medical care at the Philadelphia VAMC, Pittsburgh VA, and University of Pennsylvania (current goal of N=150; original planned N=300) who are on daily doses of prescription opioids and screen positive for risky alcohol use will be randomized to standard care (SC) or to 12 months of the adaptive prevention intervention (API) described above. The primary outcome at each follow-up point will be a dichotomous measure of alcohol use status (any risky alcohol use since the prior follow-up: yes/no). Secondary outcomes will include self-reported frequency of heavy drinking, biological measures of heavy drinking, urine toxicology tests to assess other drug use, opioid overdoses, depression, and pain.

Objectives and Hypotheses

a. Primary objective: To compare the effectiveness of a 12-month adaptive prevention intervention (API) with standard care (SC) over an 18-month follow-up period, for veterans treated with prescription opioids and who are engaging in risky/hazardous drinking, as defined by NIAAA guidelines. Note that the inclusion criteria have been modified to enroll veterans with a lower level of alcohol use and those who do not admit to alcohol use.

- *Hypothesis 1*: API will produce better outcomes than SC, as indicated by lower rates of risky/hazardous alcohol use across the follow-up period.

b. Secondary objectives: To examine secondary outcome measures, moderator effects, and mediation effects:

- *Hypothesis 1*: API will produce better outcomes than SC on frequency of heavy drinking, biological measures of heavy drinking (i.e., GGT and CDT), urine toxicology tests to assess other drug use, depression, and pain.
- *Hypothesis 2:* Rates of opioid overdoes will be lower in API than in SC
- *Hypothesis 3*: Intervention effects will be greater in higher-risk veterans, including those with higher prescription opioid dosages, co-occurring benzodiazepine use, poor social support, and low readiness for change.
- *Hypothesis 4*: Results favoring API over SC on risky drinking will be mediated by greater readiness for change, self-efficacy, and coping.

Progress Toward Year 5 Milestones:

Milestone	Base Line Plan Date
Task 1: Prepare the text messaging system for the study, and finalize all manuals for the adaptive prevention intervention (API)	15-Oct-2014
Task 2: Pilot test methods to identify veterans with chronic pain who are receiving daily opioid medication through VANC pharmacy records, and the screening procedures to detect risky alcohol use in these individuals	15-Oct-2014
Task 3: Complete training for the two prevention counselors in API, and identify and begin training a third prevention counselor	15-Oct-2014
Task 4: Begin enrollment of study participants	15-Jan-2015
Task 5: Complete enrollment of study participants	01-May-2017
Task 6: Complete all 18-month follow-ups	15-Oct-2018
Task 7: Complete and submit all main outcome papers	30-Jun-2019

The primary milestone for Year 5 was to have completed all 18 month follow ups. We have clearly not achieved this milestone and with our no cost extension, we will be continuing to recruit through 01-October-2019, and finish follow up visits by 01-October-2020. In an effort to increase recruitment, we also enrolled some veterans who were taking opioids for pain, but reported no alcohol use. This had been suggested and approved by the DoD, because there was reason to believe that some veterans who were drinking likely felt uncomfortable reporting this initially, but might at a later date. These veterans were placed in a "watchful waiting" group, and followed up at the regular follow-up points. If they reported alcohol use at a follow-up, they would then be added to the outcome analyses. Also, to increase our sample size, we continued to recruit through the six month of the 18 month NCE. This meant that a small number of participants were followed to 12 months, but not to 18 months (N=14). At this point, we have completed all follow-ups that were possible under this restriction and have conducted the primary outcome analyses and a majority of the secondary outcomes and analyses (see below).

Recruitment Activities

Total Recruitment Activities

- **CMCVAMC**
  - **Reviewed 4,622 electronic medical records to identify potentially eligible Veterans with 1,855 eligible to receive letters**
  - **Mailed 1,643 letters**
  - **Completed 1,144 Screens**
    - Positive screens (N=159)

Result	N	%
Enrolled	74	46.5
Met Criteria for Moderate or Severe Use Disorder	1	0.6
Does Not Meet Criteria for Risky/Hazardous Alcohol Use	3	1.9
Not Interested	32	20.1
Not Taking Prescription Opioids	3	1.9
No Show to Baseline	46	28.9
Total	159	

    - Screening/Enrollment Failures (N=985)

Reason	N	%
Not Interested	436	44.3
Does Not Have A Cell Phone	21	2.1
Does Not Meet Criteria for Risky Alcohol Use	387	39.3
Not Taking Prescription Opioids	53	5.4
Met Criteria for Moderate or Severe Use Disorder	35	3.6
Other	53	5.4
Total	985	

      - Enrolled Veterans: 74
      - Prevention Intervention: 39
        - Of which 7 were watchful waiting (i.e., not drinking at baseline)
      - Brief Intervention Only: 35
        - Of which 10 were watchful waiting
      - Completed Study: 39
      - Lost to Follow Up Prior to COVID Pandemic: 5
      - Unable to Complete Due to COVID Pandemic: 22
      - Withdrawn: 5
      - Deceased: 3 (all in Brief Intervention only condition)

- **University of Pennsylvania**
  - Reviewed 3,509 UPHS electronic medical records to identify potentially eligible Veterans
  - Screened Veterans: 311
    - Positive Screens: 61
      - Randomized: 29
    - Screening & Enrollment Failures: 282

Reason	N	%
Does not have a cell phone	3	1
Does not meet criteria for risky alcohol use	6	2.1
Found ineligible at Baseline	4	1.4
Met criteria for moderate or severe use disorder	9	3.2
No show to baseline	13	4.6
Not a veteran	4	1.4
Not drinking	1	0.4
Not Interested	156	55.3
Not taking prescription opioids	66	23.4
Unreachable	9	3.2
Waiting to Schedule	1	0.4
Other	10	3.5
Total	282	

- Enrolled Veterans: 29
- Prevention Intervention: 16
    - Of which 7 were watchful waiting
- Brief Intervention Only: 13
    - Of which 4 were watchful waiting
- Completed Study: 8
- Lost to Follow Up Prior to COVID Pandemic: 9
- Unable to Complete Due to COVID Pandemic: 10
- Withdrawn: 2

- **Pittsburgh VA**
    - Reviewed 657 electronic medical records to identify potentially eligible Veterans
        - 252 eligible for provider email
            - 24 eligible for letter
        - 405 ineligible
            - 153 on hold (expired or discontinued opioid prescriptions, not yet on opioids for three months, did not have an upcoming appointment with a prescriber)
            - 25 AUDC = 0
            - 222 not eligible
            - 4 Other
        - Number of PCP's contacted: 55
        - 250 Emails Sent

Email Correspondences	N	%
Provider Asked Patient and Willing to Be Contacted/Interested	25	10
Provider Asked Patient and Not Willing to Be Contacted/Declined	30	12
Provider Did Not Respond to Correspondence	158	63.1
Provider Contacted/Responded But Was Seeing Another Colleague/Provider	3	1.2
Provider Forgot to Ask	8	3.2
Provider Not Willing to Ask	2	0.8
Provider Tried Calling Patient But Could Not Reach	4	1.6

Patient No Showed	8	3.2
Provider Deemed Patient Ineligible/Do Not Contact	4	1.6
Patient Cancelled Appointment	8	3.2
Total	250	

- Screened Veterans: 32
  - Positive Screens (N=9)

Result	N	%
Enrolled	5	55.6
Not Interested	1	11.1
No Show to Baseline	3	33.3
Total	9	

  - Screening/Enrollment Failures (N=23)

Reason	N	%
Not Interested	11	47.8
Does Not Have a Cell Phone	1	4.3
Does Not Meet Criteria for Risky Alcohol Use	4	17.4
Not Taking Prescription Opioids	1	4.3
Met Criteria for Moderate or Severe Use Disorder	3	13
Does not have Chronic Pain	1	4.3
Other	2	8.7
Total	23	

  - Enrolled Veterans: 5
    - Prevention Intervention: 3
    - Brief Intervention Only: 2
    - Completed Study: 2
    - Lost to Follow Up: 3

Total Enrollment (across all three sites) Updated numbers

- Enrolled: 108
  - Prevention Intervention: 58
    - 14 remained in Watchful Waiting (i.e., no drinking at baseline)
  - Brief Intervention Only: 50
    - 14 remained in Watchful Waiting
  - **Completers: 49**

Regulatory Activities
No new Regulatory Activities

Opportunities for Training and Professional Development
Nothing to report

Dissemination of Results
Nothing to report

4. Impact

Development of the principal discipline of the project:
Nothing to report

Other disciplines:
Nothing to report

Technology transfer:
Nothing to report

Society beyond science and technology:
Nothing to report

5. Changes/Problems

Changes in approach and reasons for change

Recruitment Strategies
As discussed above, recruitment did improve somewhat as a result of changes in recruitment strategy discussed in past reports. We also text messaged participants at Penn appointment reminders to help decrease missed baseline visits as well as missed follow up visits.

Recruitment Sites
We closed the Pittsburgh VA recruitment site early. Pittsburgh failed to improve recruitment. The last enrolled participant at Pittsburgh was enrolled 01 May 2018. Pittsburgh only screened 9 participants in the last year. Per IRB Requirements, Pittsburgh had to follow a lengthy process prior to initiating contact with a Veteran. Pittsburgh had to keep track of potentially eligible Veterans' clinic appointments. When a potentially eligible Veteran has a PCP appointment, the research coordinator had to send an email to the provider and ask the provider if they will present the study to the Veteran. If the provider presents the study to the Veteran and he/she is interested, the research coordinator may reach out to the Veteran and offer to do a phone screen. There are a handful of PCP providers that gave permission for the study team to send a recruitment letter to their Veterans. For Veterans whose PCP has opted in to recruitment letters, Pittsburgh still had to email and ask the provider to present the study to the Veteran, but if the provider failed to present the study then a letter could be sent to the Veteran. After two weeks have passed the research coordinator could then cold call the Veteran. We believe that this lengthy process prior to initiating contact with the Veteran was a challenge to recruitment and prevented Pittsburgh from being able to recruit at expected rates.

Actual or anticipated problems or delays and actions or plans to resolve them
Recruitment has been a problem for this study despite extensive efforts.
Changes that had a significant impact on expenditures
Nothing to report

Significant changes in use or care of human subjects
Nothing to report

6. Products
Nothing to report

7. Participants & Other Collaborating Organizations

Name:	James McKay, Ph.D.
Project Role:	PI
Research Identifier (e.g. ORCID ID):	

Nearest person month worked:	2.52
Contribution to project:	Dr. McKay is directing this research project, which includes chairing weekly staff meetings, preparing all study reports, supervising staff working on the study, representing the study in discussions with the VA and other organizations, coordinating efforts to address problems that emerge, and presenting information about the study and results in professional meetings and publications.
Funding Support:	

Name:	Kate Acker
Project Role:	Student Worker
Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to project:	Ms. Acker assisted with data entry and recruitment and screening. Left position 11/30/18.
Funding Support:	
Name:	Martin D. Cheatle, M.D.
Project Role:	Co-Investigator
Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to project:	Dr. Cheatle is an expert in the treatment of pain, and he has led efforts to recruit participants from pain clinics, provided consultation on issues related to the assessment and management of pain, participated in regular staff meetings, and contributed to the writing of reports. Completed work 6/30/20.
Funding Support:	

Name:	Katherine Crockett
Project Role:	Research Coordinator
Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	9
Contribution to project:	Ms. Crockett has completed amendments to the VA and Penn IRBs, supervised research technicians, monitored the quality and accuracy of data collected, engaged in problem solving around recruitment issues, worked with the Penn Data Analytics Center to assist with recruitment, obtained UPHS patient lists and screened medical records to identify potential participants, and attended all staff meetings. – Terminated 6/30/19.
Funding Support:	

Name:	Conor Crowley
Project Role:	Project Assistant

Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to project:	Mr. Crowley has provided administrative support for the study. He assists in preparing scientific and financial reports and processes purchase orders and payments to subcontractor. No longer on project 9/30/20.
Funding Support:	

Name:	Brenda Curtis, Ph.D.
Project Role:	Co-Investigator
Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to project:	Dr. Curtis has provided expertise in the use of text messaging for behavioral health. She provides ongoing input on the text messaging program we are using in the intervention, led efforts to use Craigslist and Facebook to recruit participants, and attended all staff meetings. Dr. Curtis worked with PI and staff Left Penn 1/31/19.
Funding Support:	
Name:	Remona Gary
Project Role:	Research Scheduler
Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to project:	Ms Gary worked with research tech and participants to schedule appointments. Completed work 7/26/20.
Funding Support:	
Name:	April Howard
Project Role:	Prevention Counselor
Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	7
Contribution to project:	Ms. Howard has provided the prevention intervention to study participants, attended all staff meetings, contributed to the development of the text messaging and counseling components of the intervention, and completed all required VA trainings and documentation of clinical contacts. Left Penn 10/31/19.
Funding Support:	

Name:	Megan Ann Ivey
Project Role:	Coordinator
Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	9
Contribution to project:	Ms. Ivey has been the coordinator for the study. She has completed protocol amendments to the VA and Penn IRBs, supervised research technicians, monitored the quality and

	accuracy of data collected, engaged in problem solving around recruitment issues, and attended all staff meetings. Completed work 9/30/20.
Funding Support:	
Name:	Margaret Lawlace
Project Role:	Research Tech
Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	7
Contribution to project:	Ms. Lawlace has screened potential participants, enrolled participants, conducted baseline and follow-up interviews, tracked participant progress over time, provided information to determine which track participants in the active intervention were placed in, generated data for quarterly and yearly reports, and facilitated connections between study participants and counselors. Left Penn 5/13/2018.
Funding Support:	

Name:	Henry Kranzler
Project Role:	Co-Investigator
Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to project:	Dr. Kranzler has participated in staff meetings, provided expertise on interactions between opioids and other medications, and contributed to discussions regarding ways to increase recruitment. Work completed 7/31/19.
Funding Support:	
Name:	Kevin Lynch, Ph.D.
Project Role:	Statistician
Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to project:	Dr. Lynch has contributed to discussions about research design and statistical analyses, and provided updated power calculations to address reduced sample size. Completed work on project 9/30/20.
Funding Support:	

Name:	Linda Mangino
Project Role:	Manager of Administration and Finance
Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to project:	Ms. Mangino is responsible for reviewing and ensuring the site and prime compliance. She reviews study activities and transactions for accuracy and allowability. Ms. Mangino sets up sub-ward sites with contracts and manages invoicing. Left project 8/31/20.
Funding Support:	

Name:	David Oslin, M.D.
Project Role:	Co-Investigator
Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to project:	Dr. Oslin has participated in staff meetings and contributed to discussions regarding ways to increase recruitment. In his role at the VA as the Chief of Behavioral Health, he has facilitated connections with various groups at the VA (e.g., Internal Medicine/Primary Care) to facilitate the successful implementation of the study. Completed project 6/30/2018.
Funding Support:	
Name:	Christopher Petro
Project Role:	Data Manager
Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to project:	Mr. Petro manages the Data Management Unit and oversees the database infrastructure wherein study data is entered and maintained. Completed work 9/30/20.
Funding Support:	

Name:	Janelle Purnell
Project Role:	Research Tech
Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	8
Contribution to project:	Ms. Purnell has screened potential participants, enrolled participants, conducted baseline and follow-up interviews, tracked participant progress over time, provided information to determine which track participants in the active intervention were placed in, generated data for quarterly and yearly reports, and facilitated connections between study participants and counselors. Left project 9/13/20.
Funding Support:	
Name:	Sarah Rosenbach
Project Role:	Research Tech
Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	12
Contribution to project:	Ms. Rosenbach has identified and screened potential participants, enrolled participants, conducted baseline and follow-up interviews, tracked participant progress over time, provided information to determine which track participants in the active intervention were placed in, generated data for quarterly and yearly reports, and facilitated connections between study participants and counselors. Left Penn 6/19/16.
Funding Support:	

Name:	Dana Stefany
Project Role:	Student Worker
Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	10
Contribution to project:	Ms. Stefany has screened potential participants, enrolled participants, conducted baseline and follow-up interviews, tracked participant progress over time, provided information to determine which track participants in the active intervention were placed in, generated data for quarterly and yearly reports, and facilitated connections between study participants and counselors. Left Penn 6/30/19.
Funding Support:	
Name:	Max Stern
Project Role:	Research Tech
Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	9
Contribution to project:	Mr. Stern has screened potential participants, enrolled participats, conducted baseline and follow-up interviews, tracked participant progress over time, provided information to determine which track participants in the active intervention were placed in, generated data for quarterly and yearly reports, and facilitated connections between study participants and counselors. Left Penn 8/31/2017.
Funding Support:	
Name:	Tyrone Thomas
Project Role:	Prevention Counselor
Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	7
Contribution to project:	Mr. Thomas has provided the prevention intervention to study participants, attended all staff meetings, contributed to the development of the text messaging and counseling components of the intervention, and completed all required VA trainings and documentation of clinical contacts. Ended on 9/30/20.
Funding Support:	
Name:	Stephanie Urena
Project Role:	Research Tech
Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	7.4
Contribution to project:	Ms.Urena has screened potential participants, enrolled participants, conducted baseline and follow-up interviews, tracked participant progress over time, provided information to determine which track participants in the active intervention were placed in, generated data for quarterly and yearly reports, and facilitated connections between study participants and counselors. Position ended 5/12/2019.

Funding Support:	

Name:	Barry VanGrift
Project Role:	Project Assistant
Research Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to project:	Mr. Vandergrift has provided administrative support for the study. He assists in preparing scientific and financial reports and processes purchase orders and payments to subcontractor. Left Penn 4/1/2018.
Funding Support:	

Name:	Deborah Van Horn, PhD
Project Role:	Coi-Invesitgator
Research Identifier (e.g. ORCID ID):	Dr. Van Horn collaborated on the planning of data analyses, interpretation of results, and report writing. She will also prepare clinical materials, supervise study prevention counselors, and quantify adherence to treatment protocols. She was instrumental in the development of the telephone interventions, and has been the clinical coordinator for the PI's three prior treatment studies at the Penn. Dr. Van Horn is certified as a MI trainer. Left Penn 3/31/16.
Nearest person month worked:	2
Contribution to project:	
Funding Support:	

Change in active other support of the PD/PI(s) or senior/key personnel since last reporting period:

OTHER SUPPORT

McKay, J

ACTIVE

W81XWH-14-1-0060 (McKay) 04/01/14 – 09/30/20 1.2 calendar months nce
DOD (nce)
Preventing risky drinking in veterans treated with prescription opioids
The major goals of this project are: 1) To compare the effectiveness of a 12-month integrated prevention intervention with standard care over an 18-month follow-up period, for veterans treated with prescription opioids and who are engaging in risky/hazardous drinking, as defined by NIAAA guidelines; and 2) To examine secondary outcome measures, moderator effects, and mediation effects.
Role: Principal Investigator

K24-DA029062-6 (McKay) 05/01/17 – 04/30/22 4.32 calendar months
NIDA
Adaptive Treatment Models for the Management of Drug Use Disorders
The proposed competing renewal grant provides support to Dr. James McKay to sustain and expand his mentoring of postdoctoral fellows and new clinical investigators conducting patient oriented research in the addictions. The grant will also support new research, which builds on Dr. McKay's current research program on the development and evaluation of adaptive approaches to continuing care.
Role: Principal Investigator

R01-AA025539 (Witkiewitz) 07/01/17 – 06/30/22 .36 calendar months
NIAAA/UNM Sub.
Mechanisms of behavior change in alcohol use disorder treatment

The data analysis grant involves combining data from seven completed clinical trials and developing and testing new methods to study mediation effects in the treatments included in these trials.
Role: Subaward Principal Investigator

U34 DA045177 (Kampman) 08/01/18-07/31/21 .36 calendar months
NIH/NIDA
Remote observed dosing to improve Suboxone compliance in clinical practice
This project proposes to develop and test the use of remote compliance monitoring of Suboxone to improve medication adherence and treatment outcomes.

R01-AA025957 (Brooks) 04/01/18 – 02/28/21 .6 calendar months
NIAAA/ PHMC Sub.
Can a group relapse prevention tool kit enhance fidelity in community treatment?
The proposed project will test the effectiveness of a toolkit to facilitate the use of cognitive-behavioral therapy (CBT).
Role: Subaward Principal Investigator

R21 – AAA027571 (Ertefaie) 06/15/19-05/31/21 1.08 calendar months
NIAAA/University of Rochester Sub
1R21AA027571
Optimal dynamic treatment strategies for controlling alcohol use: novel methods for selecting and incorporating effect modifiers
This project aims to address the need for robust, rigorous and efficient methods for estimating optimal treat-ment strategies in high-dimensional settings that paves the way for future studies of advancing personalized medicine by discovering genetic and phenotypic subgroups who respond favorably to experimental compounds. To this end, we propose to develop advanced statistical machine learning methods for detecting effect modifiers and providing valid inference for the resulting decision rules.
Role: Subaward Principal Investigator

UF1-MH121944 10/01/19-09/30/24 1.2 calendar months
(Mandell, Bogner & Kampman)
NIH/NIMH
The whole health study: collaborative care for OUD and mental health conditions
The major goals of this project is to refine and rigorously test a collaborative care model for patients with opioid use disorder (OUD) and major depression, post-traumatic stress disorder, or an anxiety disorder in primary care. We also will examine clinical practice characteristics associated with successful implementation and the cost effectiveness of different care models.
Role: Co-investigator

R01 DA048764-01 (Ertefaie) 09/01/19-08/31/23 .6 calendar months
NIH/NIDA (subcontract)
Analyzing sequential, multiple assignment, randomized trials (SMART) in the presence of partial compliance
The broad objective of this project is to develop methodologies that can be used to adjust for noncompliance in SMARTs. Specifically, we address several fundamental unsolved problems: 1) estimating the outcome mean under different design embedded ATSs in SMARTs; 2) estimating the optimal deeply tailored ATSs that take into account subjects' ongoing performance and if followed lead to an optimal outcome. The proposed methods are motivated by and applied to two SMARTs: The Adaptive Approach to Naltrexone Treatment for Alcoholism, and the Adaptive Treatment for Cocaine Dependence. Each of these studies consists of ~50% non-compliers, which could seriously affect the concluding results.
Role: Subaward Principal Investigator

TRI/PHMC (Festinger/Dugosh) 06/01/19-05/31/23 .6 calendar months
Pennsylvania State Grant

Agreement No. 7604052303
Enhancing the office-based buprenorphine treatment: An adaptive psychosocial approach
This project aims to provide a mechanism to further increase the long-term efficacy of office-based opioid treatment (OBOT) using a personalized, patient-centered adaptive approach to the delivery of psychosocial treatment.
Role: Co-Investigator

University of Washington (Saxon) 06/01/19-06/30/21 .6 calendar months
NIDA CTN 3UG1-DA-013714 (subcontract)
Pacific Northwest Node
Further development and evaluation of the Brief Addiction Monitor for use in measure based care
There is interest in whether the Brief Addiction Monitor (BAM) could be shortened, while maintaining good psychometric properties. Here, we put forward a brief plan to develop both a short form version of the BAM as well as a very brief version that could be used in primary care. A shorter instrument, which retained the three content areas of the current BAM (e.g., substance use, risk factors, protective factors), was seen as more feasible for measurement-based care in opioid treatment programs. However, even a shorter version of the BAM was thought to be unworkable in primary care-based MAT. To be truly feasible in primary care, an instrument would need to be even shorter, around 4-5 items at most.
Role: Subaward Principal Investigator
OVERLAP

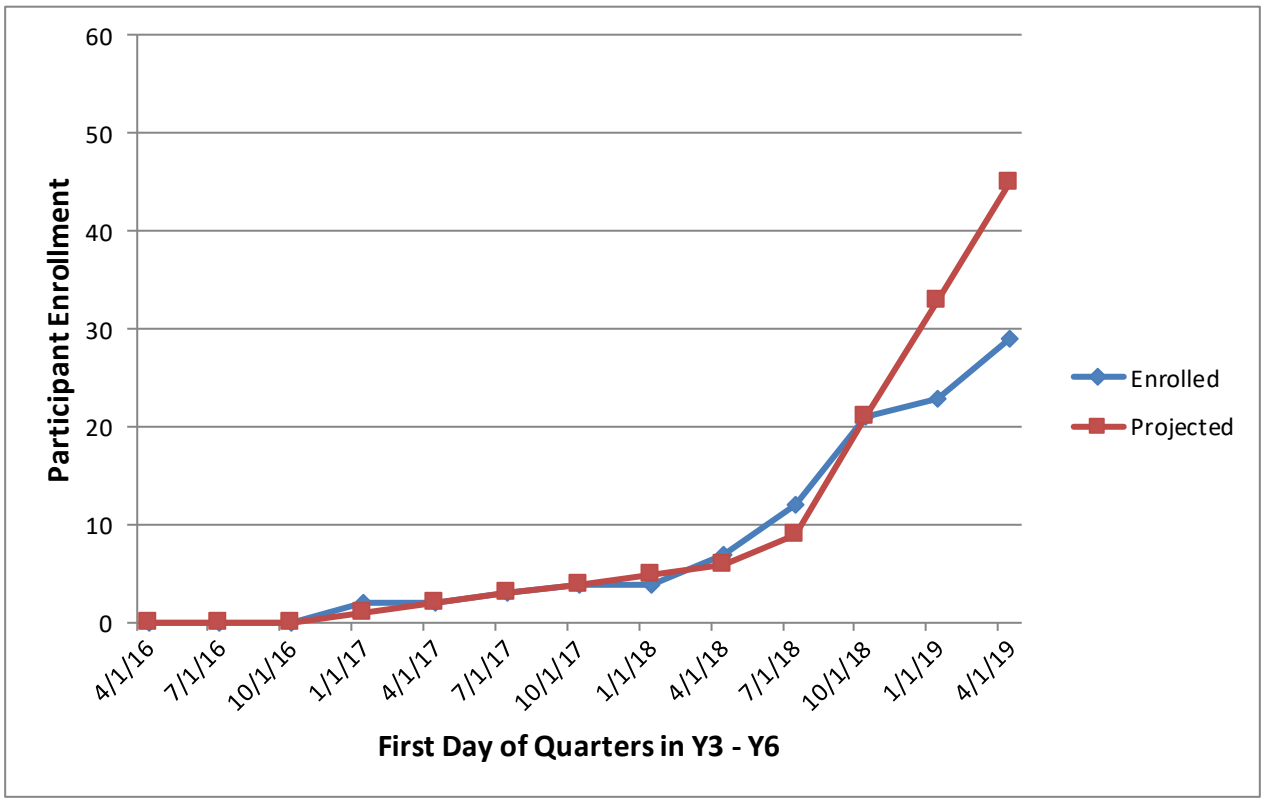
There is no scientific or budgetary overlap.
In the event a new proposal is funded the budgets will be adjusted appropriately in conjunction with agency staff. Effort of the K24 can be reduced to 3.0 CM if necessary.

8. Special Reporting Requirements
Attached- see Quad Chart

9. Appendices
a. University of Pennsylvania Enrolled Versus Projected Recruitment
b. CMCVAMC Enrolled Versus Projected Recruitment
c. Pittsburgh VA Enrolled Versus Projected Recruitment
d. Report of Initial Outcome Analyses

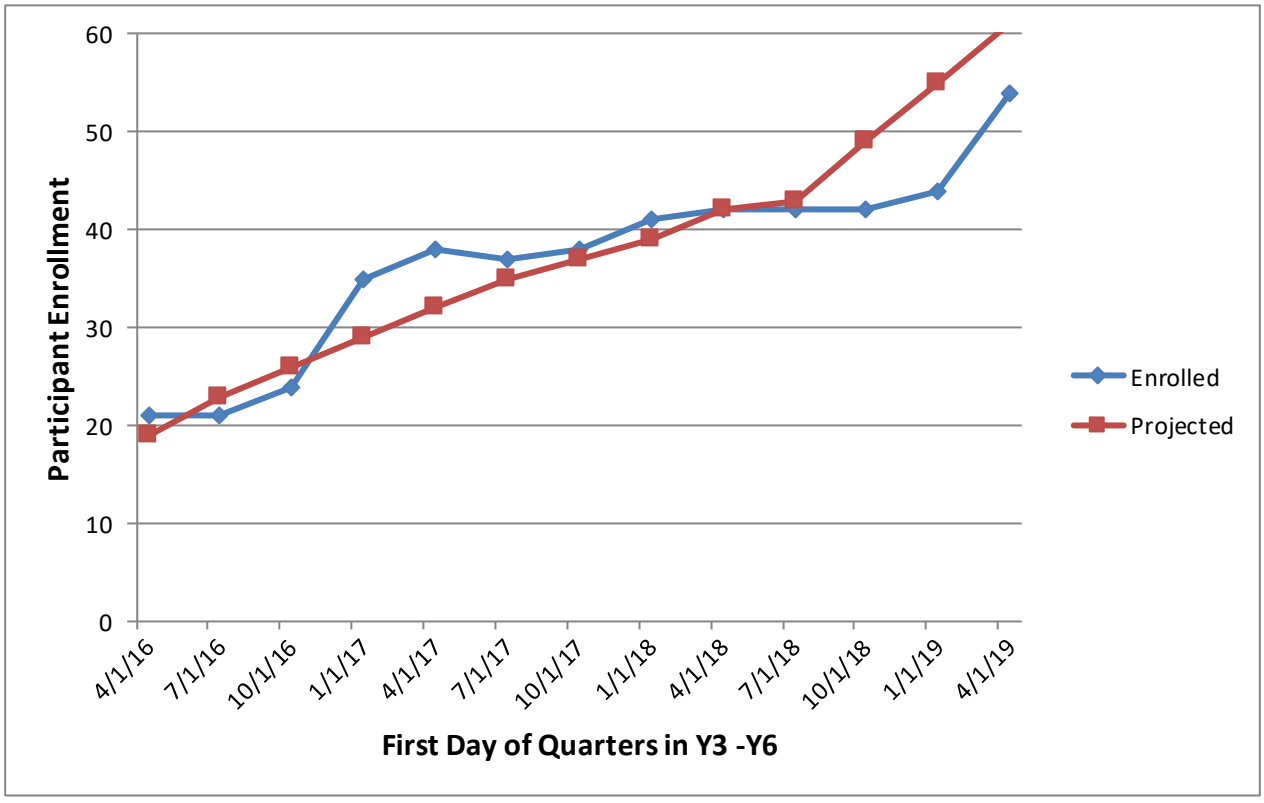
APPENDIX A

University of Pennsylvania Enrolled Versus Projected Recruitment



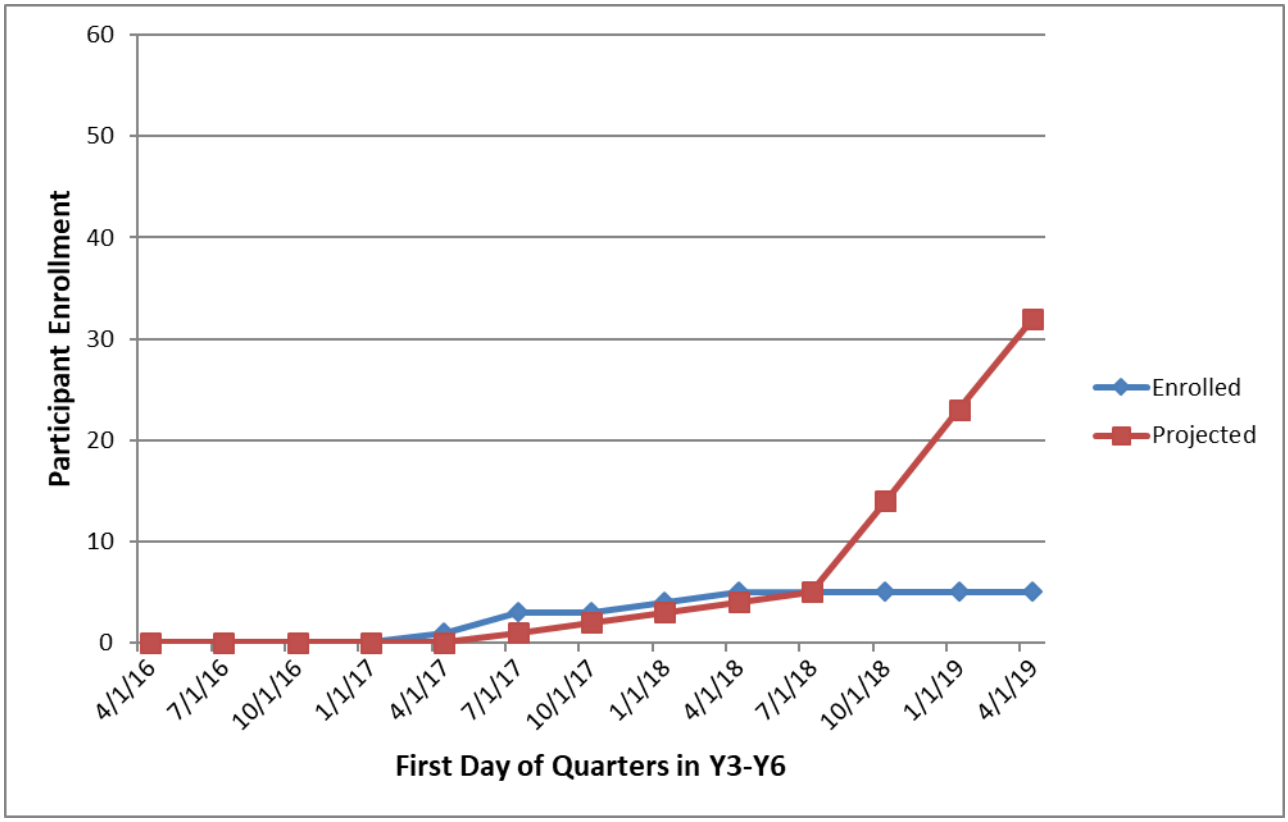
APPENDIX B

CMCVAMC Enrolled Versus Projected Recruitment



APPENDIX C

Pittsburgh VA Enrolled Versus Projected Recruitment


60
50
40
30
20
10
0
Participant Enrollment
4/1/16
7/1/16
10/1/16
1/1/17
4/1/17
7/1/17
10/1/17
1/1/18
4/1/18
7/1/18
10/1/18
1/1/19
4/1/19
First Day of Quarters in Y3-Y6
Enrolled
Projected

Appendix D: Report of Initial Outcome Analyses

Here, we present preliminary outcomes that address research follow-up rates, analyses of the primary outcome measure (i.e., frequency of risky drinking) and five secondary outcomes (i.e., percent days heavy drinking, urine toxicology, depression, pain, and mortality). The study objectives and hypotheses were as follows.

Objectives and Hypotheses

a. Primary objective: To compare the effectiveness of a 12-month adaptive prevention intervention (API) with standard care (SC) over an 18-month follow-up period, for veterans treated with prescription opioids and who are engaging in risky/hazardous drinking, as defined by NIAAA guidelines. Note that the inclusion criteria have been modified to enroll veterans with a lower level of alcohol use and those who do not admit to alcohol use.

- *Hypothesis 1*: API will produce better outcomes than SC, as indicated by lower rates of risky/hazardous alcohol use across the follow-up period.

b. Secondary objectives: To examine secondary outcome measures, moderator effects, and mediation effects:

- *Hypothesis 1*: API will produce better outcomes than SC on frequency of heavy drinking, biological measures of heavy drinking (i.e., GGT and CDT), urine toxicology tests to assess other drug use, depression, and pain.
- *Hypothesis 2:* Rates of opioid overdoes will be lower in API than in SC
- *Hypothesis 3*: Intervention effects will be greater in higher-risk veterans, including those with higher prescription opioid dosages, co-occurring benzodiazepine use, poor social support, and low readiness for change.
- *Hypothesis 4*: Results favoring API over SC on risky drinking will be mediated by greater readiness for change, self-efficacy, and coping.

Due in large part to issues stemming from the COVID-19 pandemic, we do not yet have access to some of the secondary outcome variables (e.g., biological measures of alcohol use and opioid overdose data from the VA electronic medical record). In order to not further delay this final report, we are submitting it now with results for the primary outcome, frequency of risky drinking, and five of the secondary outcomes. Because of the smaller than expected final sample size, we will likely not be able to complete the planned moderator analyses (Secondary objective, hypothesis 3). Most of the moderators themselves are poorly distributed, which further compounds the small overall sample size problem. We plan to conduct work to construct a single measure of risk, which will incorporate the measures we were planning on examining individually, and include it in future moderator analyses. But that work is beyond the scope of this preliminary report of outcomes. In addition, given the lack of treatment group effects, we are also not conducting mediator analyses at this time (Secondary objective, hypothesis 4).

Retention in study.

Of the randomized sample of 80 participants, 38 (47.5%) make all five assessment visits; for the 44 participants in the Intervention group, 23 (52.3%) made all visits, compared to 15 of 36 (41.7%) in the Standard Care group (Chi-square (1) =0.89, p=0.34, OR=1.53, 95% CI=[0.63, 1.73]). Therefore the odds of completing all research follow-ups was 53% higher in the intervention group than in the standard care group, although that difference was not statistically. The follow up rate at 18 months was reduce by the fact that the last 14 participants entered into the study were not eligible to complete an 18 month follow-up because the study ended.

The mean number of visits made in the groups was 4.09 (SE=0.21) in the intervention group, compared to 3.53 (SE=0.31) in the Standard Care group, a non-significant difference (Kruskal-Wallis Chi-square (1) =1.49, p=0.22). Although not a significant difference, it is notable that the follow-up rate in the Intervention group was consistently 10 percentage points higher than that in the standard care group.
The retention rates (as percentages of the original group size) at the various assessment points, based on UDS and TFB data, are as follows:

	3	6	9	12	18
Standard Care	81%	81%	78%	72%	42%
Intervention	93%	93%	89%	82%	52%

There was no significant difference between the groups on time to dropout (Log-Rank Chi-square (1) =1.29, p=0.26). It should be noted that the large drop off in follow-up rates at month 18 was due both to attrition and to the fact that participants enrolled in the study during the final six months of recruitment were not in the study long enough to be eligible for an 18 month follow-up (N=14) prior t the end of the NCE.

Primary Outcome: Risky Drinking Weeks

For each subject, we counted the number of weeks in which any risky occurred in each of the 3-month study periods. The means and standard errors for each group for each period are as follows:

Month	Standard Care	Intervention	Cohen's d
1-3	3.03 (0.83)	2.46 (0.65)	0.14
4-6	2.97 (0.76)	2.15 (0.55)	0.21
7-9	2.96 (0.79)	2.44 (0.65)	0.13
10-12	3.85 (1.03)	2.50 (0.66)	0.30
13-15	2.68 (1.07)	2.14 (0.75)	0.13
15-18	4.60 (1.31)	2.70 (0.91)	0.42

We compared the groups on the number of risky weeks per three-month period using a GEE Poisson regression model, with working correlation structure of compound symmetry, and using robust standard errors. The mean number of risky weeks per period in the Standard Care group was 1.30 (95% CI= (0.72, 2.34)) times higher than the corresponding mean in the Intervention group, a non-significant difference (Chi-square (1) =0.69, p=0.41). Although not significant, the advantage of the intervention group over standard care got larger toward the end of the follow-up, reaching the level of a moderate effect size in months 10-12 and months 15-18. For example, in months 15-18, the intervention reduced the number of weeks with risky drinking by almost half (i.e., 2.7 weeks vs. 4.6 weeks with risky drinking over a 3 month period).

Secondary Outcome 1: Percent days heavy drinking (PDHD)

The mean of PDHD for the control group ranged from 7.7% to 16.1%, compared to a range of 9.6% to 13.5% for the Intervention group. The PDHD variable was heavily skewed towards higher values, so we compared the groups on the square-root of PDHD. The means and standard deviations for the groups (square root values), and the Cohen's d, for each period, are as follows:

Month	Standard Care	Intervention	Cohen's d
1-3	1.59 (2.43)	1.86 (3.21)	-0.10
4-6	1.92 (2.76)	1.99 (3.05)	-0.03
7-9	1.89 (2.71)	1.62 (2.69)	0.10
10-12	2.09 (2.80)	1.87 (2.78)	0.08
13-15	1.86 (2.13)	1.73 (2.62)	0.05
15-18	2.65 (3.12)	2.10 (2.46)	0.20

We used a GEE regression model, with working correlation structure of compound symmetry, and using robust standard errors. Across the period, the Intervention group had slightly higher mean value of the square-root transformed PDHD variable (b=0.01, SE=0.50, 95% CI=[-0.97, 0.99]), a non-significant difference (Chi-square (1) =0.00, p=0.98).

Secondary Outcome 2: Drug use as measured by UDS

The percentage of each group with a UDS positive for amphetamines, barbiturates, benzodiazepines, cocaine, or opiates for each of the assessments are as follows:

Month	Standard Care	Intervention	OR	p-value
Baseline	27%	36%	0.67	0.44
3mo	38%	35%	1.10	0.36
6mo	35%	44%	0.69	0.50
9mo	41%	36%	1.23	0.73
12mo	41%	38%	1.17	0.81
18mo	50%	42%	1.38	0.65

A GEE logistic regression model, with working correlation of compound symmetry and robust standard errors, showed no significant difference between the groups: Chi-square (1) = 0.14, p=0.71, OR = 1.18, 95% CI = (0.50, 2.79). Of the 92 positive urine samples obtained, 62 included a positive opiate test. The other drugs with some evidence of use were cocaine (14 positive tests) and benzodiazepines (19 positive tests). It is not yet clear how many of the positive tests for opiates were due to use of prescribed medication. Further work will be required post COVID to determine this.
.

Secondary Outcome 3: Depression – PHQ-total
The means and standard errors for each group for each period are as follows:

Month	Standard Care	Intervention	Cohen's d
Baseline	6.34 (0.80)	7.61 (0.90)	-0.24
3	7.93 (0.93)	8.87 (0.94)	-0.18
6	7.48 (0.92)	9.26 (1.07)	-0.32
9	8.12 (0.94)	9.00 (1.18)	-0.16
12	7.53 (1.08)	9.07 (1.13)	-0.29
18	6.07 (1.10)	8.54 (1.19)	-0.49

We compared the groups on the mean of the PHQ total score per three-month period using a GEE regression model adjusting for baseline PHQ total, with working correlation structure of compound symmetry, and using robust standard errors. There was a significant Condition by month interaction (Chisquare (1) =3.85, p=0.0497): the (baseline adjusted) estimated mean was lower for the Intervention group than the Standard Care group for months 3 and 6 (by -0.51 and -0.05, respectively) and higher for the later months (by 0.40, 0.66 and 1.77, respectively. None of the within-month differences were statistically significant (p=0.06 for month 18, and p>0.25 for all other months)

Secondary Outcome 4: Pain – BPI Average Pain and Pain Interference score
<u>BPI Average Pain</u>
The means and standard errors for each group for each period are as follows:

Month	Standard Care	Intervention	Cohen's d
Baseline	7.33 (0.32)	7.55 (0.31)	-0.11
3	6.63 (0.38)	7.24 (0.40)	-0.28
6	7.04 (0.40)	6.83 (0.42)	0.09
9	6.88 (0.41)	7.07 (0.32)	-0.10
12	6.79 (0.54)	6.71 (0.46)	0.03
18	6.67 (0.68)	7.42 (0.39)	-0.33

We compared the groups on the mean of the BPI Average Pain score per three-month period using a GEE regression model adjusting for baseline BPI Average with working correlation structure of compound symmetry, and using robust standard errors. Neither the month by group interaction (Chi-square (1) =0.36, p=0.55) nor the main effect of Condition (Chi-square (1) =0.08, p=0.77) were significant.

<u>BPI Pain Interference Score</u>
The means and standard errors for each group for each period are as follows:

Month	Standard Care	Intervention	Cohen's d
Baseline	38.11 (2.38)	36.18 (2.44)	0.13
3	37.15 (2.86)	39.24 (2.60)	-0.14
6	37.68 (2.83)	41.37 (2.44)	-0.26
9	38.72 (3.14)	37.13 (2.88)	0.10
12	35.84 (3.62)	36.87 (3.33)	-0.06
18	39.87 (3.49)	36.17 (2.83)	0.27

We compared the groups on the mean of the BPI Pain Interference score per three-month period using a GEE regression model adjusting for baseline BPI Interference with working correlation structure of compound symmetry, and using robust standard errors. Neither the month by group interaction (Chi-square (1) =0.41, p=0.53) nor the main effect of Condition (Chi-square (1) =0.84, p=0.36) were significant.

Secondary Outcome 5: Mortality and overdoses
During the course of participation in the study, three veterans died. All three were in the standard care group, with none in the intervention group. We have not yet been able to access VA electronic medical records to assess rates of hospitalizations due to overdoses.

Summary
None of the primary or secondary hypotheses that we were able to test was supported by significant findings. The adaptive prevention condition did not produce better outcomes than standard care on frequency of weeks with risky drinking, days with heavy drinking, drug use as measured by urine drug screens, depression, or pain. However, there were several findings suggestive of a positive intervention effect; weeks with risky drinking were somewhat higher in the standard care condition toward the end of the follow-up (e.g., in months 9-12 and 15-18, a moderate effect size), and there were three documented deaths in the standard care as compared to none in the intervention condition. Moreover, the follow-up rate was consistently higher by about 10 percentage points in the intervention condition. Biological drinking measures and VA electronic data base outcomes have not yet been examined. Due to the small sample size and lack of treatment effects, we did not conduct the planned moderator and mediator analyses. However, we will construct a single "prognosis" moderator made up of the individual moderator variables and run one test of moderation.

We will prepare a manuscript with the complete results for submission to a peer reviewed journal. Give the lack of more positive findings so far, we will probably not engage in efforts to disseminate this intervention within the VA or DoD at this time. However, a final decision on dissemination will await the results of final and complete data analyses.

Preventing risky drinking in veterans treated with prescription opioids

NH130003 and
W81XWH-14-1-0060

PI: James McKay, Ph.D. **Org:** University of Pennsylvania **Award Amount:** $3,501,673

Study/Product Aim(s)

- Determine the efficacy of a 12 month integrated prevention intervention (IPI for the reduction of hazardous alcohol use in veterans treated with prescription opiates for pain.
- Examine impact of the intervention on secondary outcomes, including other drug use, depression, pain, and overdose rates
- Test whether effects are greater in certain groups: veterans with higher opiate dosages, co-occurring benzodiazepine use, poor social support, and low readiness to change

Approach

Randomized trial comparing IPI to standard VA care in 300 veterans treated with opiate medications for pain. Alcohol, other drug, depression, and pain outcomes will be examined in six follow-ups over an 18 months period. IPI is an adaptive intervention, in which veterans who do not respond to the initial prevention efforts receive additional prevention services

Insert a picture or graphic here, with a caption, that represents the proposed work

Accomplishments: initiated recruitment; added the Pittsburgh VA as a second site, began enrollment of veterans in Philadelphia area who are not receiving services at the VA, maintained a > 80% follow-up rate, intervention is being delivered with good fidelity to the manual and outcomes in veterans receiving the intervention are good.

Timeline and Cost

Activities	CY 14	15	16	17	18	19	20
Complete protocol, enroll subjects							
Continue enrollment/follow-ups							
Continue follow-ups, conduct initial data analyses							
Complete enrollment;follow-ups							
Estimated Budget ($K)	$504	$602	$570	$524	$603	$461	$237

Updated: 03/15/21

Goals/Milestones

CY14 Goal – Complete all preparatory work, begin enrollment of Ss☑ Prepare IRB submission, hire staff, complete prevention manuals **CY15 Goals** – Continue Ss enrollment, initiate follow-ups
☐Enrolled 50% of study sample, maintain an 80% follow-up rate
☐Achieve good adherence to prevention intervention protocol **CY16 Goal** – Complete enrollment, continue follow-ups
☐Achieve projected sample size, maintain 80% follow-up rate **CY17 Goal** – Continue follow-ups and begin data analyses
☐Maintain 80% follow-up rate, examine within-intervention outcomes
CY18 Goal – Continue follow-ups and begin data analyses **Comments/ Challenges/Issues/Concerns**
CY19 Goal
CY 20 NCE

- Recruitment rate has improved
- NCE CY 20

Budget Expenditure to Date

Final Expenditure for NCE: $227,830.67
Final Expenditures for period 04/1/14– 09/30/20 $3,494,038.98