COLLABORATING TO HEAL ADDICTION AND MENTAL HEALTH IN PRIMARY CARE (CHAMP)

STATISTICAL ANALYSIS PLAN (SAP)
1/24/2023

Multiple Principal Investigators - John Fortney, PhD; Andrew Saxon, MD; Anna Ratzliff, MD

Authors – Brittany Blanchard, PhD, Patrick Heagerty, PhD, John Fortney, PhD
Version – 5.0 (8/30/2024)

Grant Number: UF1MH121942
National Clinical Trial (NCT) Identified Number: NCT04600414
Sponsor: National Institute of Mental Health (NIMH)

Modifications to the CHAMP Statistical Analysis Plan

Change	Reason	Date
In shell Table S2 changed "*Change to 3 months"* to *"3 months*" and "*Change to 6 months (primary outcome)*" to "*6 months (primary outcome)*"	To simplify the calculation of the SE for the adjusted mean differences in order to calculate the confidence interval	5/6/24
Replacing adjusted mean difference with AOR for opioid use primary outcome	Calculating SE for adjusted means from logistic model requires use of the delta method, so	6/18/24

Reporting Cohen's d without confidence intervals	confidence intervals are less interpretable (i.e., contain 0 for significant effects) We will report confidence intervals for the AOR. (see above regarding calculating SE for logistic model).	6/18/24
Test moderated mediation by analyzing moderation first	Because we planned to conduct these analyses separately (mediation, then moderation), the presence of a moderation of M→Y violates an assumption of mediation.	8/8/24
Added mean, standard deviation, and 95% confidence intervals to secondary outcomes table (Table S3). Omitted recent overdose covariate from main models.	To provide additional detail to assist with interpretation of secondary outcome results. To help with model convergence.	8/30/24

Table of Contents

1. Introduction

In 2018, the National Institute of Mental Health (NIMH) issued a Request For Applications (RFA-MH-19-525) titled "Helping to End Addiction Long-term (HEAL) Initiative: Effectiveness Trials to Optimize, Implement, Scale, and Sustain the Collaborative Care Model for Individuals with Opioid Use Disorders and Mental Health Conditions". Four clinical trials were funded, including the Collaborating to Heal Addiction and Mental Health in Primary care (CHAMP) trial described in this manuscript. The objective of the CHAMP trial was to compare the effectiveness of a Collaborative Care Model (CoCM) intervention designed to co-manage both Opioid Use Disorder (OUD) and common co-occurring Mental Health Symptoms (MHS) to a usual care control condition representing CoCM designed to manage co-occurring MHS only.

This statistical analysis plan (SAP) will comprehensively enumerate the primary and secondary outcomes, and mediating variables, and corresponding analyses.

2. Study design

The CHAMP hybrid type 2a effectiveness-implementation trial was a cluster randomized trial in which clinics were randomized to CoCM for OUD and MHS or CoCM for MHS only. Hybrid type 2a trials compare two clinical interventions and pilot test a practical, but not evidence-based, implementation strategy.

Randomization - Initially 24 clinics were stratified according to one of two CoCM fidelity cohorts (specified as low or high) and healthcare organization and then randomized in a 1:1 ratio by our statistician into one of two arms (intervention or control). Stratification served two purposes. First, stratifying on healthcare organization (each has 2 or 4 clinics in the study) should balance the intervention and control groups according to key system level factors that influence quality and outcomes (e.g., electronic health record quality). Second, stratifying on cohort ensures balance with regard to fidelity to the CoCM model which is likely to be correlated with our primary outcomes. In addition, clinics with lower fidelity were designated to have a longer training duration. An additional 18 clinics were recruited later during the study and they all received the short training duration in order to maximize recruitment, and therefore we did not stratify the randomization of the additional 18 clinics by fidelity but did continue to stratify by health care system.

3. Outcomes

Primary outcome. There are two primary outcomes (see Table 1). Opioid use is one of our primary outcomes and is measured using item 7E from the Brief Addiction Monitor-Revised (BAM-R) which was derived from the Addiction Severity Index35 by CESATE: "7. In the past 30 days, how many days did you use any of the following drugs: E. Opiates (e.g., Heroin, Morphine, Dilaudid, Demerol, Oxycontin, oxy, codeine (Tylenol 2,3,4), Percocet, Vicodin, fentanyl, etc.)?" Our other primary outcome is mental health related quality of life and is being measured using

the Veterans Short Form Health Survey 12 Mental Health Component Summary score (MCS). Both primary outcomes are assessed at the 6-month follow-up survey.

Secondary outcomes. This study includes 24 secondary outcomes, assessed at both the 3-month follow-up and the 6-month follow-up (Table 1). Secondary outcomes include the use of other drugs, depression, anxiety, PTSD, pain, physical health-related quality of life and perceived access to OUD care (see Table 1). Secondary outcomes also include opioid use and mental health related quality of life assessed at the 3-month follow-up survey. Exploratory outcomes are risk factors for premature mortality, including suicidal ideation, discontinuing MOUD, overdose, suicide attempts, emergency department admission, and hospitalization. Risk factors are collected via survey and adverse event reporting.

Table 1. Primary and Secondary Outcomes

Construct/Instrument	**Instrument(s)**	**Baseline**	**3-Month Follow-Up**	**6-Month Follow-Up**
Multiple Primary Outcomes				
Opioid Use	BAM-R[1,2]	X	X	X
Mental health related quality of life (MCS)	Veterans Short Form-12[3]	X	X	X
Secondary Outcomes				
Pain	PEG[4]	X	X	X
Alcohol Use	AUDIT-C[5]	X	X	X
Cannabis Use	BAM-R[1,2]	X	X	X
Other Drug Use	BAM-R[1,2]	X	X	X
Depression	SCL-20[6]	X	X	X
Anxiety	PROMIS Measure - Anxiety, Short Form[7,8]	X	X	X
PTSD	PCL-5[9,10]	X	X	X
Physical health related quality of life (PCS)	Veterans Short Form-12[3]	X	X	X
Access to Care	APAC[11]	X	X	X
Exploratory Outcomes				
Risk factors for mortality	WFS[1] and Adverse Events	X	X	X
Mediator Variable				
MOUD Consistency	WFS[1]	X	X	X

APAC - Assessment of Perceived Access to Care
BAM-R - Brief Addiction Monitor-Revised
ICR - Individual Change Readiness
MOUD – Medications for Opioid Use Disorder

PCL-5 - PTSD Check List
PC-PTSD-5 – Primary Care PTSD Screen for DSM-5
PCS - Physical health related quality of life
PEG - Pain, Enjoyment of Life and General Activity
PTSD – Posttraumatic Stress Disorder
SCL-20 - Hopkins Symptom Checklist
WFS – Written For Study

Mediator variables
The hypothesized mechanism of action is engagement in MOUD, which we define as initiation and "*consistent*" refilling of the MOUD medication, which has been demonstrated to be correlated with good outcomes.[12] MOUD consistency is defined as the ratio of the number of days they reported taking the MOUD medication (numerator) to the number of days during the reporting period for which it was prescribed (denominator).[12] This is measured from self-reported MOUD use in the past 30 days which is assessed using survey questions written for the study.

4. Analyses

4.1. Primary and Secondary Outcomes (Hypotheses 1 and 2)

Hypothesis 1: Compared to patients with MHS and OUD at clinics randomized to the control, patients at clinics randomized to the intervention group will report better access to and engagement in OUD treatment, less opioid use (primary outcome), better mental health functioning (primary outcome), fewer disorder specific mental health symptoms, better quality of life, and fewer risk factors for premature mortality (exploratory outcome).

All outcomes will be analyzed with a multilevel model accounting for clustering of observations (level 1) within patients (random effects at level 2) and clinics (random effects at level 3). The combined equation for the basic multilevel model applicable to a quantitative outcome such as mental health quality of life is as follows:

$$\begin{aligned} Y_{cit} = \beta_0 + \beta_1(Intervention) + \beta_2(3\ months) + \beta_3(6\ months) \\ + \beta_4(Intervention\ x\ 3\ months) \\ + \beta_5(Intervention\ x\ 6\ months) + \beta_6 DesignVars_c \\ + [u_c + u_{ci0}(baseline) + u_{ci3}(3\ months) + u_{ci6}(6\ months)] \end{aligned} \quad \text{(Eq. 1)}$$

where $_c$ = clinic, $_i$ = patient, $_t$ = time
$_{t0}$ = baseline
$_{t3}$ = 3-month follow-up

$_{t6}$ = 6-month follow-up

Here the outcome measured at time t, for subject i, in clinic c is denoted by Y_{cit}. To account for the cluster-randomization this model includes a random effect for each clinic denoted as u_c. In order to allow a general longitudinal correlation and variance structure we use three subject-specific error terms denoted by u_{cit} for t=0, 3, 6 months. We assume a general 3x3 covariance model for these error terms to provide maximal validity to inference regarding change over time. To allow for potential non-linear change over time, we will enter time as a nominal variable by including dummy codes for the 3 and 6 month time points represented by the variables $(3\ months)$ and $(6\ months)$. Intervention main effects and interaction between intervention and time indicators capture the difference between intervention clinics and control clinics at each wave – with β_1 representing the adjusted mean difference across intervention groups at baseline (adjusting for the design variables) -- with $\beta_1 + \beta_4$ representing the adjusted mean difference across intervention groups at 3 months – and with $\beta_1 + \beta_5$ representing the adjusted mean difference across intervention groups at 6 months. Therefore, the primary contrasts are given by with β_4 as the 3-month intervention effect, and β_5 as the 6-month intervention effect. Note that each intervention effect accounts for the potential imbalance of outcomes across the intervention and control groups at baseline due to the small number of clusters (β_1) and this is removed from the cross-sectional mean contrasts at each follow-up time to define the key intervention effect parameters. *DesignVars* denotes a vector of covariates that includes: 1) low vs high fidelity, which must be controlled because it was a design/stratification variable for some clinics, and 2) additional covariates theoretically related to both the primary outcome and the probability of not completing follow-up surveys which will aid in enhancing validity against missing data and improving precision of estimation. Specifically, we will include: 1) worried about not have stable housing in the next two months, 2) being on parole or probation and/or presently awaiting charges, trial or sentencing, 3) opioid craving, 4) pain, 5) Audit-C, 6) provider trust (APAC item #6), and 7) any use of other drugs (dummy coding for each class of drug). The pre-specified primary effect of interest will be β_5, which represents the difference in change from baseline between intervention and control clinics at 6 months. Table S2 presents a shell table for the primary outcome and Figure 2 presents a shell plot. Table S3 presents a shell table for the secondary outcomes.

For the primary outcome (mental health related quality of life [0-100]) we will use a linear mixed model with a normal distribution with a linear link function and model structure given above in Equation 1. For the primary outcome days-using-opioids [0-30] we will modify the above linear mixed model and adopt a similar regression structure using a generalized linear mixed model with binomial distribution logit link function. We will retain the random effect structure to include a random effect for clinic and include the time-specific subject-level error terms to both allow for binomial overdispersion and a general longitudinal covariance over time. For the secondary and exploratory outcomes, appropriate link functions will be used for linear, binary (logit), ordinal (logit), and count (Poisson/negative binomial depending on dispersion) data. For any binary longitudinal outcomes, we will simplify the subject-level random effects to be a simple random intercept due to identifiability (no overdispersion and only correlation).

Effect sizes. Cohen's *d* effect sizes will be calculated and presented with 95% confidence intervals. Between group effect sizes will be calculated as the model-estimated treatment effect at each time point divided by the pooled, raw baseline standard deviation.

Testing of Multiple Primary Outcomes. The intervention will be interpreted to have been successful if there is a significance group difference between either primary outcome, not necessarily both primary outcomes. Corrections for multiple testing will be computed using a Bonferroni correction for the two multiple primary outcomes and therefore we will use an alpha=0.05/2 = 0.025 to test each primary outcome. All secondary outcomes are exploratory and no multiple testing adjustment will be used. We will present secondary and exploratory outcomes descriptively using a forest plot to illustrate the collection of associations with intervention.

4.2 Moderated Mediation Analyses (Hypothesis 2)

Hypothesis 2: MOUD consistency will fully mediate any improvements in patient-reported outcomes observed in intervention clinics compared to control clinics.

These analyses will compare the different pathways through which the intervention transmits effects. We hypothesize that the intervention should lead to greater use of MOUD (A path in Figure 2) because of the care managers' encouragement of MOUD initiation and adherence, leading to improved outcomes. We also expect the intervention will cause MOUD use to be more effective (Moderation path in Figure 3) in improving outcomes because of the use of the OTRI measurement-based care instrument and dosage recommendations by the consulting psychiatrist. Because the proposed moderation violates the assumption of mediation, we will first test the moderation(Figure 3), followed by a mediation or moderated mediation analysis (Figure 2).[13,14] This analysis will be performed in three stages. In the first stage, we will use the same model as described in equation 1 to assess the MOUD consistency x intervention (moderator) interaction (Figure 3) (Table S4a). In the second stage, we will test the effect of the intervention on the mediator (A path in Figure 2) (Table S4b). In the third stage, the mediator will be included (B path), controlling for the direct effects of treatment (C path in Figure 2) (Table S4b). If the moderation is statistically significant, the MOUD consistency x intervention interaction will be included in this model . Models will be run separately for 3- and 6-months.

Figure 2. Path diagram for mediation model

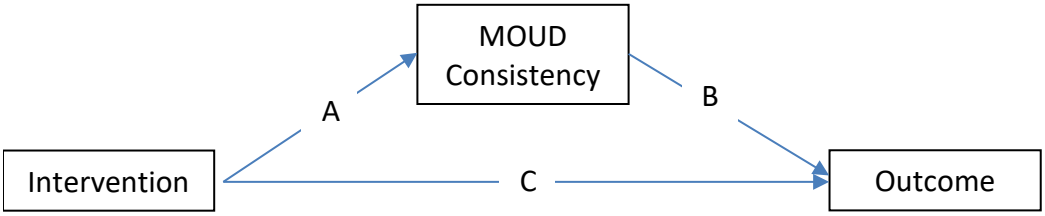
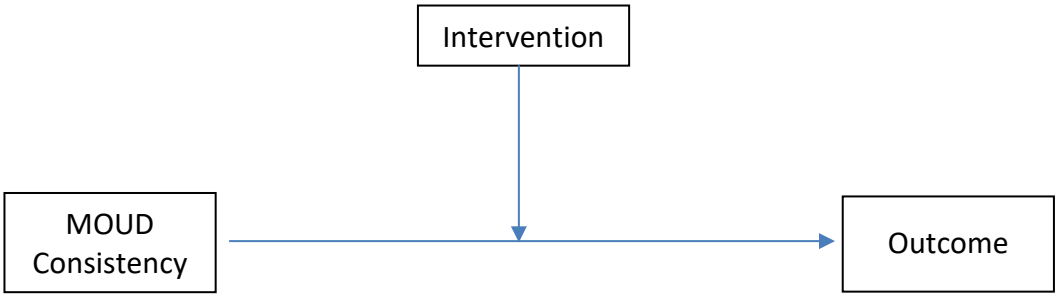


Figure 3. Path diagram for moderation model



For the moderation analysis, we use the same model structure and design variables as the primary outcome. We will include MOUD consistency and intervention as main effects and the MOUD Consistency x intervention interaction. (Table S4a).

To calculate A path, the main effect of treatment on the mediator, we will use the same model as the primary outcome (Table S4b). Direct effects on MOUD consistency (path A) will be presented as an adjusted mean. To account for the potential imbalance of the mediator across the intervention and control groups at baseline due to the small number of clusters, the main effect for intervention at baseline is included.

To calculate the B and C paths, we will include the mediator and intervention-mediator interaction in predicting outcomes (Table S4b). To calculate the total effect of the mediator for the intervention, we will sum the main effects and interactions. To calculate indirect effects (Table S4b), we will multiply the A path by the B path for the mediator. Because the distribution of the product may be non-normal, we will calculate 95% confidence intervals using bootstrapping.

5. Missing data

Estimates from multilevel models are unbiased under conditions of *Missing at Random* (MAR), which means that the mechanism that causes missingness is included in the model. Most relevant to the current analysis, in longitudinal data, estimates will be unbiased when

missingness is caused by previously observed values of the dependent variable, but not if missingness is caused by the unobserved value at the missing wave. We will attempt to make the MAR assumption more plausible by incorporating reasons for missingness into the model. We will analyze data with maximum likelihood estimation (MAR assumption) and no auxiliary information.[15]

6. Power Calculation

The DSMB directed the research team to discontinue consenting new patients into the trial for reasons of futility due to the current rate of recruitment. Therefore, we present a revised power analysis calculated before the outcome data are to be unmasked. The revised power analysis is based on the observed number of patients enrolled (n=254), observed number of clinics enrolling ≥1 patient (n=28), the observed coefficient of variation (0.97) which represents the variation in cluster sizes, and the Intraclass Correlation Coefficients (ICCs) estimated for interim analysis requested by the DSMB. For the masked interim ICC estimation we used all patient data available on 11/7/2022, including N=191 in the baseline sample and N=155 in the 6-month follow-up sample. We adjusted for treatment group and baseline primary outcomes. We used the jackknife method to compute a standard error by computing ICCs deleting each cluster in turn and then averaging these estimates.[16] For the 6-month follow-up, the opioid use ICC was estimated to be 0.00 (SE= 0.02). For the 6-month follow-up, and the MCS ICC was estimated to be 0.03 (SE=0.09). Based on these estimates, and using a Bonferroni correction to account for multiple outcomes, we will have 80% power to detect a medium effect size of 0.40 for days of opioid use and a medium effect size of 0.46 for MCS. This represents a difference of 2.65 (e.g., 15.00 days compared to 12.3 days) days using opioids and a difference of 6.22 (e.g., 40 compared to 33.8) on the MCS between the intervention and control groups.

7. References

1. Hallinan S, Gaddy M, Ghosh A, Burgen E. Factor structure and measurement invariance of the Revised Brief Addiction Monitor. *Psychological assessment.* 2021;33(3):273-278.
2. Liebmann EP, Resnick SG, Hoff RA, Katz IR. Associations between patient experience and clinical outcomes in substance use disorder clinics: Findings from the veterans outcomes assessment survey. *Journal of substance abuse treatment.* 2022;133:108505.
3. Jones D, Kazis L, Lee A, et al. Health status assessments using the Veterans SF-12 and SF-36: Methods for evaluating outcomes in the Veterans Health Administration. *Journal of Ambulatory Care Management.* 2001;24(3):68-86.
4. Krebs EE, Lorenz KA, Bair MJ, et al. Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. *Journal of general internal medicine.* 2009;24:733-738.
5. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): An effective brief screening test for problem drinking. *Archives of internal medicine.* 1998;158:1789-1795.
6. Derogatis LR. Symptom Checklist-90-Revised (SCL-90-R). In: American Psychiatric A, ed. *Handbook of Psychiatric Measures*. Washington, D.C.2000:81-84.
7. Merriwether EN, Rakel BA, Zimmerman MB, et al. Reliability and Construct Validity of the Patient-Reported Outcomes Measurement Information System (PROMIS) Instruments in Women with Fibromyalgia. *Pain medicine (Malden, Mass).* 2017;18(8):1485-1495.
8. Pilkonis PA, Choi SW, Reise SP, Stover AM, Riley WT, Cella D. Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS(R)): depression, anxiety, and anger. *Assessment.* 2011;18(3):263-283.
9. Blevins CA, Weathers FW, Davis MT, Witte TK, Domino JL. The Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5): Development and Initial Psychometric Evaluation. *Journal of traumatic stress.* 2015;28(6):489-498.
10. Bovin MJ, Marx BP, Weathers FW, et al. Psychometric properties of the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (PCL-5) in veterans. *Psychological assessment.* 2016;28(11):1379-1391.
11. Fortney JC, Pyne JM, Hawrilenko M, et al. Psychometric Properties of the Assessment of Perceived Access to Care (APAC) Instrument. *The Journal of ambulatory care management.* 2020;44(1):31-45.
12. Lo-Ciganic WH, Gellad WF, Gordon AJ, et al. Association between trajectories of buprenorphine treatment and emergency department and in-patient utilization. *Addiction (Abingdon, England).* 2016;111(5):892-902.
13. VanderWeele TJ. A unification of mediation and interaction: a 4-way decomposition. *Epidemiology (Cambridge, Mass).* 2014;25(5):749-761.
14. Muthén B, Asparouhov T. Causal effects in mediation modeling: An introduction with applications to latent variables. *Structural Equation Modeling.* 2015;22(1):12-23.

15. Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. *The New England journal of medicine.* 2012;367(14):1355-1360.
16. Efron B, Stein C. The jackknife estimate of variance. *The Annals of Statistics.* 1981:586-596.

8. Shell Tables and Figures

Table S1. Baseline characteristics of patients enrolled in SPIRIT

	Overall	Intervention Group	Control Group
	n (%) or μ (SD)	n (%) or μ (SD)	n (%) or μ (SD)
Age (years)			
Are you of Hispanic, Latino/a/e or Spanish origin?			
Yes			
No			
Missing			
Race			
American Indian, Alaska Native, or other Indigenous group			
Native Hawaiian or other Pacific Islander			
African American or Black			
White			
Multi-race			
Another Identity			
Missing			
Current Gender Identity			
Man			
Woman			
Non-binary or gender fluid			
Missing			
Marital Status			
Divorced			
Married or living with a partner			
Separated			
Single, never married			

Widowed
Missing
Sexual Orientation
Bisexual
Lesbian/Gay
Straight
Another Identity
Missing
Employment Status
Working full-time
Working part-time
Temporarily laid off or on strike
Unemployed
Retired
Disabled
Student
Missing
Poverty Threshold
Above
Below
Missing
Insurance Status
Medicaid
Medicare
Government Health Insurance Program
Private Health Insurance
None of the above forms of insurance
Missing
Military Service
No
Yes, but not currently on active duty or in the reserves

Missing

Housing Status

No, not living in stable housing

Yes, living in stable housing

Missing

Concern about Future Housing

No, not worried about housing in the near future

Yes, worried about housing in the near future

Missing

Parole/Probation

No

Yes

Missing

Awaiting charges, trial, or sentencing

No

Yes

Missing

Currently mandated by a court to receive addiction treatment

No

Yes

Missing

Individual Readiness to Change (ICR; range: 0-10)

Importance for change

Confidence for change

Readiness for change

Clinical Characteristics:

Veterans Short Form 12 Mental Health Component Summary score (MCS; range: 0-100)

Opioid Use:

Any opioid use in the past 30 days

Number of days of opioid use in the past 30 days

Opioid Craving:

Not at all

Slightly

Moderately

Considerably

Extremely

Medication for OUD:

Lifetime

Current

Alcohol Use: (AUDIT-C; range: 0-12)

Other Drug Use: Any use in the past 30 days

Cocaine and/or crack use

Other stimulant use

Sedative and/or tranquilizer use

Cannabis use

Inhalant use

Other illegal drug use

Recent Overdose Experience

Ever overdosed

Number of previous overdoses

Overdosed in the past 6 months

Number of overdoses in the past 6 months

Pain Level (PEG; range: 0-10)

Hopkins Symptoms Checklist (SCL-20; range: 0-4)

Anxiety (*PROMIS Measure - Anxiety 8a - Adult v1.0*: range: 36.4-76.8)

PTSD Checklist (PCL-5; range: 0-80)

Table S2. Multiple primary outcomes across intervention conditions

	Intervention		Control		Treatment Effects		
	Mean (SD)	95% CI	Mean (SD)	95% CI	Adjusted Odds Ratio	95% CI	Cohen's *d*
Opioid Use							
Baseline							
3 months							
6 months (primary outcome)							
					Adjusted Mean Difference	95% CI	Cohen's *d*
MCS							
Baseline							
3 months							
6 months (primary outcome)							

Table S3. Treatment effects for secondary and exploratory outcomes at 3 and 6 month follow-up

	Intervention				Control			Unstandardized Effects		Cohen's *d*	
	N	n	Mean (SD)	95% CI	n	Mean (SD)	95% CI	adj. B	*p*	*d*	95% CI
Pain, Enjoyment of Life and General Activity - PEG											
Baseline								-	-	-	-
3 months											
6 months											
Depression – SCL-20											
Baseline								-	-	-	-
3 months											
6 months											
Anxiety – PROMIS Measure – Anxiety, 8-item Short Form											
Baseline								-	-	-	-
3 months											
6 months											
PTSD – PCL-5											
Baseline											
3 months											
6 months											
Physical Health-Related Quality of Life – PCS											
Baseline								-	-	-	-
3 months											

6 months

Assessment of Perceived Access to Care – APAC

Baseline								-	-	-	-	
3 months												
6 months												

	Intervention				Control			Unstandardized Effects		Adjusted Odds Ratio	
	N	n	Marginal Probability (SD)	95% CI	n	Marginal Probability (SD)	95% CI	adj. B	*p*	AOR	95% CI
Alcohol Use – AUDIT-C											
Baseline								-	-	-	-
3 months											
6 months											
Cannabis use – BAM-R											
Baseline								-	-	-	-
3 months											
6 months											
Other illegal drugs – BAM-R											
Baseline								-	-	-	-
3 months											
6 months											

Table S4a. Moderation analysis

	adj. B	SE	95% CI
Intervention Group			
MOUD Consistency Predicting Opioid Use			
3 months			
6 months			
MOUD Consistency Predicting MCS			
3 months			
6 months			
Control Group			
MOUD Consistency Predicting Opioid Use			
3 months			
6 months			
MOUD Consistency Predicting MCS			
3 months			
6 months			

Table S4b. Mediation analysis

	adj. B	SE	95% CI
Intervention Predicting MOUD Consistency			
3 months			
6 months			

MOUD Consistency Predicting Opioid Use

3 months

6 months

MOUD Consistency Predicting MCS

3 months

6 months

Indirect Effects

Intervention-> MOUD Consistency-> Opioid Use

3 months

6 months

Intervention-> MOUD Consistency-> MCS

3 months

6 months