2021

Development and Evaluation of Video-Based Directly Observed Therapy for Office-Based Treatment of Opioid Use Disorders with Buprenorphine

NCT03779997

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Trial of Adherence Application for Buprenorphine Treatment (TAAB) Study Protocol and Statistical Analysis Plan

1 Study Overview and Design

The objective of this study is to compare an innovative mobile health (mHealth) platform to support patients treated for opioid use disorder (OUD) with buprenorphine to treatment-as-usual (TAU). The application will provide video-based directly observed therapy (video-DOT) which may result in better health outcomes for patients and less public health risk for diversion.

All participants will follow the same visit schedule. Interviews will occur at baseline (Week 0) and the final visit (Week 12) and assessments will include questions on current and prior substance use, treatment history, medication adherence, drug diversion, general physical and mental health and treatment satisfaction. A point of care urine drug test (UDT) will also be administered at baseline and all weekly visits which will assess for opioids and other substances. Research staff will review the electronic medical record at baseline and week 12 to assess engagement in treatment. Additionally, at 24 weeks post-enrollment the research staff will complete a review of the electronic medical record and record engagement in clinic treatment, changes in buprenorphine treatment during the study period and the results of clinical urine drug testing if available.

Study type: Pilot Randomized Controlled Trial of a Behavioral Intervention – Video-DOT smartphone application where participants will be asked to record one daily video of themselves confirming daily ingestion of their prescribed buprenorphine.

Primary Purpose: Treatment

Interventional Study Model: Parallel Assignment

Number of Arms: 2

1.1 Target Population

1.1.1 Study Sites

Subjects will be recruited at office-based buprenorphine programs at Harborview Medical Center (University of Washington) and Boston Medical Center (Boston University).

1.1.2 Inclusion/Exclusion Criteria

Inclusion criteria

1) ≥18 years old

2) Receiving oral (i.e. not injectable) buprenorphine treatment at an office-based buprenorphine program at Harborview Medical Center or at Boston University Medical Center for ≤4 weeks.

3) Willing to be randomized to either video-DOT or TAU arms.

Exclusion criteria

1) Unable or unwilling to use smart phone (phones to be provided as needed)

2) Cognitive impairment (acute or chronic) resulting in inability to provide informed consent

3) Researcher's discretion that participant will not be appropriate for participation in the study (e.g. participant is planning on moving away, is knowledgeable of future incarceration during study, or has behavioral issues that may pose safety concerns for clinic and research staff)

4) Inability to read and understand English as needed for following in app instructions

1.2 Group Allocation – Randomized

This study is a randomized controlled trial with two arms - TAU and intervention with the application (video-DOT). Group assignment will be randomized through computer randomization procedures using REDCap and randomization lists generated with the random number generator in R. Randomization will be stratified by site (HMC v. BMC). Each site was allotted 99 treatment assignments with half for TAU and half video-DOT in case of potential recruitment and enrollment imbalances between sites (it is anticipated that there will be approximately 40 enrolled participants at each site). The target total sample size is 80. The PIs will be blinded to randomization; other research staff (e.g., research coordinator and assistant) will not be blinded.

1.3 Study Outcomes

Primary Outcome – Percentage of 12 research study UDTs that are negative for opioids between 1 week and 12 weeks post-randomization

Secondary Outcome – Engagement in treatment at week 12

Exploratory Outcomes

1. Engagement in treatment at week 24
2. Number of consecutive weeks with study UDTs negative for opioids during the 12-week study period
3. Self-report of use of illicit opioids in the past 30 days assessed at week 12
4. Percentage of days adherent to buprenorphine by self-report during the 12-week study period
5. Time to occurrence of non-retention
6. Having one or more study UDTs negative for buprenorphine any time during the 12-week study period
7. Having a study UDT positive for stimulants (cocaine, amphetamines or methamphetamines) at week 12
8. Patient satisfaction with treatment at week 12

2 Sample Size Determination

We anticipate that 70% of patients will complete the 12-week intervention period of our pilot trial, and that the percentage of opioid negative urine samples will be approximately 50% in the TAU arm.

The sample size of 80 patients is estimated to provide 69% power to detect the anticipated difference of 20% in the rate of opioid negative samples. The minimal clinically meaningful difference is considered to be 15%, which would require approximately 200 patients to reliably detect.

The final sample size for the Phase III trial will be determined based on the results of the pilot trial.

3 Analysis Plan

3.1 Analysis Parameters

Results of the Generalized Estimating Equations (GEE), Poisson regression, and unequal variance t-test analyses will be reported with 95% confidence intervals and test of the null hypothesis at a significance level of 0.05.

GEE was selected because it accounts for correlation between observations on the same patient over time without requiring assumptions about correlation structure by using "robust" variance estimates.

3.2 Primary Analysis (Percentage Opioid Negative Urine Tests)

The primary analysis is performed to test the following hypothesis:

Primary Hypothesis: Patients in video-DOT arm will have higher percentage of weekly UDTs negative for opioids compared to TAU during the 12 -week intervention period.

Analyses will be done according to the intent-to-treat principle which includes all randomized patients regardless of their compliance with the study protocol. To evaluate the primary hypothesis, we will compare percentage of negative UDTs between the two groups using Generalized Estimating Equations (GEE). Missing urine samples will be assumed to be positive*.

* **NOTE**: As of 3/13/2020 phone visits have occurred at both sites due to the COVID-19 outbreak. For follow-up and final assessment visits by phone, a study UDT sample was not collected. If a clinical UDT result is also not available for a particular phone visit, then the participant's UDT data for that visit is excluded from the primary analysis.

Primary Outcome Variables

12 Research-UDTs for 5 Opioid Assays (F/U Visits 1-11, and Final):

- Negative for opioids* = negative for the following: Morphine (i.e., "udt_he"), Methadone, Oxycodone, Fentanyl
  * Propoxyphene assay was in the original UDTs (Alere iCup); New UDT (Identify Diagnostics) does not include it. Will not include this data in the analysis. Dates new UDT's first started being used: BMC – 11/6/2019, UW – 11/8/2019.

  (1) On 2/11/2020 a decision was made to code a study UDT as negative if at least one substance was missing but the rest were negative.
    (a) **Note**: First check the clinical UDT to supplant a missing value. I.e., If the clinical UDT is also missing for that same substance, code the test as negative. If the clinical UDT

is positive for the particular substance that is missing from the study UDT, then code that test as positive.

3.3 Secondary Analysis (Retention - Week 12)

The secondary analysis is performed to test the following hypothesis:

Secondary Hypothesis: Patients in video-DOT arm will be more likely to be engaged in office-based treatment with buprenorphine at the conclusion of the 12-week intervention period.

To evaluate the secondary hypothesis, we will use Poisson regression with robust standard errors to compare treatment groups on the proportion of participants engaged in treatment at 12 weeks (i.e. still receiving medication). The results of this analysis will be expressed as a percentage difference for video DOT compared with TAU.

Secondary Outcome Variables

1. Week 12 Post-Enrollment EHR Review (Medication information)

2. Final visit – Participant self-reports continuing treatment by confirming that they have not stopped receiving buprenorphine prescription from healthcare provider.

Additional analyses will be conducted to compare Self-Report and EHR data for patients who have both data points to assess validity.

3.4 Exploratory Hypotheses

1. **Retention – 24 weeks post-randomization**
    - **Hypothesis**: Patients in video-DOT arm will be more likely to be engaged in office-based treatment with buprenorphine at 24 weeks post-randomization
        - To evaluate, we will use **Poisson regression with robust standard errors** to compare treatment groups on proportion of participants engaged in treatment at 24 weeks (i.e. still receiving medication) the results of this analysis will be expressed as a percentage difference for video-DOT compared with TAU. Results will be reported as a difference between proportions of patients engaged in treatment.
    - **Outcome Variable**
        - Week 24 Post-Enrollment EHR Review (Medication information and discharge information)

2. **Consecutive Weeks Opioid Negative Urine Tests – 12-week intervention period**
    - **Hypothesis**: Patients in video-DOT arm will have a higher number of consecutive weeks with research UDTs negative for opioids (non-buprenorphine) from baseline to 12 weeks post-randomization than TAU arm.
        - To evaluate, we will use **t-test with unequal variance** to compare the mean number of consecutive weeks with negative UDTs between treatment arms. Results will be reported as an estimate of the difference in means.

- **Outcome Variable:**
    - 12 Research-UDTs for 5 Opioid Assays (F/U Visits 1-11, and Final) negative for all of the following:
        - Morphine, Methadone, Oxycodone, Fentanyl

3. **Opioid Use Self-report – Final visit**
    - **Hypothesis**: At final visit, patients in video-DOT arm will self-report fewer days using illicit opioids in the past 30 days than TAU arm.
        - To evaluate, we will use a **Poisson regression with robust standard errors** to compare treatment groups on proportion of participants who self-report use in past 30 days at week 12. Results will be reported as a difference between proportions of participants who report illicit opioid use at week 12.
    - **Outcome Variable**:
        - Final Visit – ASI Past 30 days w/o prescription or in greater amounts than prescribed (i.e. illicit use)
            - Heroin, Buprenorphine, Methadone, Fentanyl, Other prescription opioids

4. **Buprenorphine Adherence Self-Report – 12-week intervention period**
    - **Hypothesis**: Patients in video-DOT arm will self-report higher percentage of days adherent to their prescribed buprenorphine between Baseline and 12 weeks post-randomization than TAU arm.
        - To evaluate, we will use **Poisson regression with robust standard errors** to compare treatment groups on participants' proportion of self-reported days adherent to buprenorphine over the 12-week intervention period. Results will be reported as a comparison between groups on the percentage of days adherent.

    - **Outcome Variables:**
        - F/u 1 -11 Visit – Adherence Follow-up Timeline Follow-back
        - Final – Treat Final (i.e. Adherence final) Timeline Follow-back

5. **Time to occurrence of non-retention (discharge) – 24 weeks post-randomization**
    - **Hypothesis**: Patients in video-DOT arm will have longer time to discharge than TAU arm from baseline to 24 weeks post-randomization
        - To evaluate, we will use **Kaplan-Meier survival curves** and a log-rank test. Results will be reported using a hazard ratio.
    - **Outcome Variable**:
        - 24 Week Post-Enrollment EHR Review – Discharged (Y/N) and Date of Discharge

6. **Buprenorphine Non-Use – 12-week intervention period**
    - **Hypothesis**: Patients in video-DOT arm will have a lower percentage of at least one weekly study UDT negative for buprenorphine than TAU arm over the 12-week intervention period.

- To evaluate, we will use **Poisson regression with robust standard errors.** Results will be reported as a difference in percentage of having at least one UDT negative for buprenorphine.
- **Outcome Variable**:
  - F/U 1-11, Final Visits – 12 Research UDT Buprenorphine assay results

7. **Stimulant Use – Final visit**
   - **Hypothesis**: At final visit, patients in video-DOT arm will have a lower percentage of UDTs positive for stimulant substances than the TAU arm.
     - To evaluate, we will use **Poisson regression with robust standard errors** to compare the percent of patients' UDTs positive for stimulants.
   - **Outcome Variables**:
     - Final Visit – Research UDT Stimulant Panels
       - Positive for stimulants = positive for Cocaine, Amphetamines, or methamphetamines. If "missing" count as positive.

8. **Treatment Satisfaction – Final visit**
   - **Hypothesis**: At final visit, patients in the video-DOT arm will report higher satisfaction with clinic's treatment of OUD than TAU arm.
     - To evaluate, we will use **t-test with unequal variance.** Results will be reported as a difference between mean satisfaction scores (1-5).

   - **Outcome Variable**:
     - Final Visit – Likert Scale – Participant's satisfaction with clinic helping participant manage their OUD
       - Likert Scale Options
         1. Very Dissatisfied
         2. Dissatisfied
         3. Neutral
         4. Satisfied
         5. Very Satisfied

3.5 Sensitivity Analyses

The primary analysis will be repeated for each of the following modifications:

1. **Adjusted Analyses**: We will use Generalized Estimating Equations to compare percentage of negative UDTs with adjustment for the following covariates: (see table below)

2. **Missing Data Analyses**: The primary analysis will be repeated using multiple imputations for missing urine samples (rather than assuming all missing are opioid positive). All covariates listed below will be used in the imputation model provided they have less than 20% missing. (See additional details on missing data in Section 3.8.)

3. **Per-protocol Analyses**: The primary analysis will be repeated excluding patients who drop out of the study or are not compliant with study protocol (e.g., submitted 7 or less videos during the first 4 weeks of study involvement). In addition, analyses will use the number of uploaded videos as a measure of compliance to determine whether there is a dose-response effect.

4.

Covariate Table	
1. Site	Seattle or Boston
2. Age	Years
3. Sex	Male, Female
4. Race	Caucasian vs. Non-Caucasian
5. Hispanic Ethnicity	Yes or No
6. Education	Less than High School, High School, Some College, Bachelor's degree or higher
7. Prior Buprenorphine Treatment	Yes or No
8. Homelessness	Yes or No

3.6 Additional Model Selection Analyses

Additional analyses will be completed using different models (linear and logistic) to determine which models will be best suited for a future definitive trial.

3.7 Sub-group Analyses

The primary analysis will be repeated with interaction terms between treatment arm and each of the following sub-group variables:

a. Site (Boston and Seattle)
b. Gender (Men vs. Women)
c. Age (based on median split)
d. Baseline homelessness

Results will be reported as treatment effect estimates for each sub-group with 95% confidence intervals and tests of the null hypothesis with overall level of significance 0.05 and Bonferroni adjustment for multiple comparisons. In addition, a significance test of the interaction between treatment and each sub-group variable will be conducted at significance level 0.05.

3.8 Missing Data

All efforts will be made to complete study visits/procedures and avoid missing data. However, we anticipate there will be missing data, in particular for the primary outcome. As has been the convention in other studies, we will assume that missing UDT results are positive (unless a visit was conducted by phone due to COVID-19). However, we will also conduct analyses to better understand the nature of missing data and carry out multiple imputation analysis in order to determine the impact of missing UDTs.

We will assess missing data by comparing baseline characteristics between participants lost to follow-up (who are missing data on the primary or secondary outcome) versus those who are not.

Missing data patterns will also be evaluated including the frequency and percentage of those missing for each variable and the distribution of the number of variables missing. Patterns of missing urine samples will be described and compared between treatment arms.

Data collected to the point of lost to follow-up will be compared to the data of those who complete the study to examine possible missing data mechanisms, e.g., missing completely at random (MCAR), missing at random (MAR), or not missing at random (NMAR).

Sensitivity analyses using multiple imputation will be performed to assess the possible impact of missing data on the study results for the primary and secondary analyses. Imputation models will include the baseline covariates listed in the table above as well as intermediate outcomes as appropriate (e.g., for 24-week outcomes, the 12-week outcomes can be used in imputation models).

4 Data Monitoring

4.1 Interim and Safety Analyses

No formal interim efficacy or futility analyses are planned for this research because of the low risk level of the study.

However, the study team will evaluate the progress of the study, including periodic assessments of data quality, participant recruitment, accrual and retention, and factors external to the study when interpreting the data, such as

- Scientific developments or the new availability of proven clinical services that could have an impact on the safety of the participants.
- The performance of the study or the ethics of the study.

Further information related to reporting and tracking of AEs/SAEs can be found in the TAAB Study DSMP.