Opioid Treatment and Recovery Through a Safe Pain Management Program

NCT03889418

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STATISTICAL ANALYSIS PLAN

1. **Introduction**

1.1 Study Design: Type II effectiveness-implementation hybrid stepped wedged cluster randomized trial

1.2 Main Study Outcomes

1.3 Primary

1.3.1 Odds Ratio of average morphine equivalent daily dose (MEDD) of opioid prescription ≥50 mg between study groups

1.4 Secondary

1.4.1 Comparison of study groups

- Rate Ratio for average MEDD in post-index versus pre-index periods
- Inpatient hospital admission per 1000 patients
- Emergency Department visits per 1000 patients
- Odds Ratio for new post-index documented pain agreement
- Odds Ratio for new post-index documented urine drug screening
- Odds Ratio for new post-index documented naloxone prescription order
- Odds Ratio for new post-index documented referral to non-mental/non-behavioral health specialist
- Odds Ratio for new post-index documented anti-depression medications

1.4.2 Among patients in the collaborative care intervention group

- Proportion with improvements in symptoms of depression (PHQ-9)
- Proportion with improvements in symptoms of anxiety (GAD-7)
- Change in average rating of quality of life (PROMIS-10)
- Change in average rating of pain (PEG-3)
- Change in average rating of opioid misuse (COMM-9)

2. **Main Objective:** Compare the clinical effectiveness of electronic medical record clinical decision support [EMR CDS] versus additional integrated behavioral health collaborative care management

    a. **Hypothesis 1:** higher proportion of patients who receive additional collaborative care compared to EMR-CDS only will have greater decreases in the rate of high-dose opioid prescriptions; higher rates of receiving opioid risk mitigation care (e.g. urine drug screens, naloxone, functional assessments specialty care); and greater reductions in inpatient hospitalizations and/or emergency department utilization.

3. **Randomization**

It was not pragmatic to randomize the behavioral health collaborative care intervention on the clinic/provider/patient level because clinics within a given geographic region of the health system have the same operations management team and share resources. Using computer generated random numbers, each region (cluster) was randomized to the order

of intervention roll out in 5 steps that occurred in 3 to 4-month intervals between April 2019 and May 2020.

4. Anticipated Effect Size, Power and Sample Size

In the investigators' prior study on the clinical effectiveness of electronic medical record clinical decision support (EMR-CDS usual care) for opioid prescribing, approximately 20% of patients on chronic opioid therapy had an average daily opioid dose ≥50 MEDD. Using equal baseline response rate (RR) for the usual care and behavioral health collaborative care groups, a total sample size of 372 patients are required to detect an odds ratio of 2.25, corresponding to a 50% decrease in the collaborative care group (RR=10% vs 20% in usual care), with 80% power. The total sample size averaged 11 patients in each study group within each of 35 clinics. In accordance with the cluster randomized design, the variance inflation factor $1 + (m - 1)\rho$ was incorporated, where m is the average cluster size (m=11) and ρ is the intra-cluster correlation coefficient ($\rho \leq 0.03$). Applying this inflation factor and rounding up to allow for equal group sizes across clusters resulted in a total sample size of 490 patients - 245 per group. Accounting for a potential 15% attrition rate, 578 total patients - 289 per group - were needed to attain the target sample size required to detect a 50% decrease in proportion of patients with average daily opioid dose ≥50 MEDD in the collaborative care group compared to the usual care group.

5. Statistical Analysis

Outcomes data were observed and collected in two time periods, pre-index and post-index. For the behavioral health group, the index date was defined as the date of enrollment during the study recruitment period (April 2019 to December 2021). For EMR-CDS usual care group, the index date is the first date within the study enrollment period at which a patient had been prescribed opioid medications for 90 of the previous 120 days.

Potential participants in the control arm of the study were identified from the chronic opioid health maintenance registry within the electronic health record system and propensity score matched to patients enrolled in the behavioral health arm. Baseline variables in the propensity score model were age at index event date, sex, race/ethnicity, average MEDD, anxiety, depression, and Charlson comorbidity index score. Average MEDD was calculated from opioid medication orders in the 12-month pre-index period. MEDD is calculated by determining the total daily amount of a prescribed opioid, multiplying the dose of the opioid by a conversion factor to ascertain morphine milligram equivalents and then adding up the converted dosage. Anxiety, depression, and Charlson comorbidity scores were determined from pre-index encounter diagnoses, historical problem lists, and PHQ-9/GAD-7 scores >10 documented within the electronic health record.

Study outcomes were observed and collected in two 12-month time periods defined relative to the index date, pre-index and post-index, resulting in a 2-dimensional vector of repeated measures for each outcome from each patient. All outcome models for repeated measures incorporate a random effect with unstructured covariance matrix to model within-patient variability. It was assumed that patients remained in the health system from their first observed encounter through the end of the study period. A difference-in-difference approach was utilized in which outcomes were assessed as the change in group differences from pre- to post-

index. The model included fixed effects for study group, time (pre-index, post-index), and the group-by-time interaction.

Repeat measured outcomes include average MEDD, MEDD ≥ 50, MEDD ≥ 90, and service utilization (inpatient/emergency department). These repeated outcomes are evaluated using the generalized linear mixed model approach described above with fixed effects as defined for the model. MEDD categorial outcomes are evaluated via mixed effects logistic regression models with estimates of odds ratios and difference-in-difference ratios (ratio of odds ratios). Mixed effects negative binomial regression models are used for assessing group differences in service utilization with rate ratios and difference-in-difference ratios (ratio of rate ratios).

Outcomes defined by first-time documentation of guideline concordant care for opioid risk mitigation are also evaluated using logistic regression. These outcomes are not repeated measures as they are only assessed post-index among patients with no pre-index documentation. Thus, time effects and random patient effects are omitted from the generalized linear model when evaluating new occurrences of guideline concordant care for opioid risk mitigation. The resulting logistic regression models include a single fixed effect for study group and no random effects.

Analyses were carried out using SAS version 9.4 for Windows, group comparisons are evaluated at significance level 0.05, and all estimates are presented with 95% confidence intervals.

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IRB APPROVAL – STUDY MODIFICATION

Opioid Treatment and Recovery through a Safe Pain Management Program	
Approval Date: 11/17/2023	
Investigator:	Eboni Price-Haywood
IRB ID:	2018.294
Sponsor:	NIH
IND, IDE, or HDE:	None
Modification Documents Reviewed:	• NCT03889418_SAP_10.8.2023.pdf, Category: IRB Protocol;
Research Sites:	Ochsner Baptist, Ochsner Baton Rouge, Ochsner Jefferson Highway Campus, Ochsner Kenner, Ochsner North Shore, Ochsner West Bank

IRB review of this submission determined it to be expedited:

(mm) Minor modification to the statistical analysis plan

NOTE: In conducting this study, you are required to follow the requirements listed in the Investigator Manual located in the eIRB library, federal regulations, and institutional policies.

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