Evaluating the Impact of the Bridge Clinic in Patients with Opioid Use Disorder

Statistical Analysis Plan

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Christopher J. Lindsell, PhD

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Introduction

To improve care for patients with opioid use disorder (OUD), Vanderbilt has implemented an Addiction Consult Team (ACT) and a Bridge Clinic. The primary purpose of the Bridge Clinic is to facilitate discharge for inpatients who are being considered for medications for OUD (MOUD). Specifically, the Bridge Clinic provides patients with temporary access to treatment at an outpatient clinic while they are waiting to be accepted into a long-term clinic. This document describes the statistical analysis plan for a pragmatic, single center, randomized, controlled trial designed to evaluate the impact of the Bridge Clinic on improving care for patients with active OUD. This document has been prepared prior to final data collection and unblinding. Because inpatient providers may delay discharge for patients with OUD who lack a source of outpatient care for MOUD, it is hypothesized that OUD patients referred to the Bridge Clinic will have a decreased overall length of stay, will follow up with their Bridge Clinic provider, and will have a reduction in overall costs for care.

Population and design considerations

Study Population:

Inpatients at VUH with OUD being considered for MOUD who have not used the Bridge Clinic before and who do not have a fixed outpatient plan are considered potentially eligible for this trial. If the ACT considers MOUD is clinically appropriate for the patient, the patient does not have plans for outpatient care, and the patient has not been enrolled in this study previously, they are enrolled, randomized, and offered a referral to either Bridge Clinic or treatment as usual (TAU) depending on randomization.

Study Design:

This study is designed as a pragmatic, single center, randomized, controlled trial comparing clinical outcomes between patients assigned to receive a referral to the Bridge Clinic and patients assigned to TAU.

Randomization:

Randomization occurs at the individual patient level. The Bridge Clinic can only accept a limited number of patients, so eligible patients will be randomized in a ratio so that the Bridge Clinic is at capacity. To start, the ratio will be 1:1, and can be updated as often as bi-weekly to maintain the Bridge Clinic capacity. There has been no indication or need to change the ratio during the study.

Sample Size Considerations:

We estimated about 700 patients per year would be eligible for this study, with a capacity for about 3-4 new patients a week to be seen at the Bridge Clinic. We expected about 2/3 of patients referred to the Bridge Clinic to make their first appointment. The mean length of stay was 15 days with a standard deviation of about 15 days. Assuming a reduced standard deviation of 10 days, with 700 patients a year and a 1:1 randomization ratio, we would have 80% power to detect a 3-day reduction in length of stay. If the standard deviation remains at 15 days, we would have 80% power to detect a 3.5-day reduction in length of stay. Due to COVID-19, enrollment was lower than expected and hospital inpatient experiences differed from historical data. Midway through the recruitment period, the overall, ungrouped distribution of length of stay was re-estimated based on participant experience. Based on the revised assumptions, to detect a 1.5-day

reduction in length of stay and assuming the observed common standard deviation is a good estimate, about 336 patients (168 per group) is needed to have 80% power.

Interventions

Inpatients with OUD who are deemed eligible for this trial are enrolled and randomized. The patients are randomized to one of two treatment arms:

a) Direct referral to a long-term outpatient addiction provider (TAU)
b) Referral to Bridge Clinic for temporary care while a long-term outpatient addiction provider is identified (intervention)

Endpoints

Primary Endpoint

The primary endpoint is the overall index hospital length of stay. The index length of stay is defined as the time between the admission and time of discharge during the inpatient visit when the participant is identified as being eligible for the study.

Secondary Endpoints

Multiple secondary endpoints are prespecified for this trial. Secondary endpoints are collected for 16 weeks following randomization:

a) Overall quality of life as measured by the Schwartz Outcome Scale-10 (SOS10). The SOS10 has ten questions scored on a 0 (never) to 6 (all or nearly all of the time) scale. A total score is computed as the sum across the 10 questions. If two questions are missing, a mean score can be imputed for the missing values to generate a total score. No further imputation will be used for this score. This is self-reported and captured at the 16-week follow-up call.
b) Linkage to MOUD provider, defined as attending at least one visit with a MOUD provider after discharge, assessed by self-report at 16-week follow-up call.
c) Self-reported buprenorphine-naloxone (or naltrexone) prescriptions filled (number filled) at the 16-week follow-up call.
d) Any recurrent opioid use reported at the 16-week phone call follow-up.
e) Number of recurrent opioid uses reported at the 16-week phone call follow-up.
f) Number of ED visits or readmissions to VUH 16 weeks post discharge identified in the electronic medical record.
g) Hospital and emergency department free days
    a. Hospital free days will be calculated as a count of whole days during the 16 weeks the subject is not in the hospital. If the subject dies before the end of 16 weeks, hospital free days will be equal to -1.
    b. Hospital and emergency department free days will be calculated as a count of whole days during the 16 weeks the subject is not in the emergency department or in the hospital. If the subject dies before the end of 16 weeks, emergency free days will be equal to -1.
h) Any overdose reported at the 16-week phone call follow-up.
i) Death in hospital or documented at the 16 week follow up or in the medical record.
j) Costs of care, defined as total costs for all care episodes at VUMC 16 weeks post discharge.

Exploratory Endpoints
Exploratory endpoints have been specified for patients with infection suitable for outpatient antibiotic therapy (OPAT) management. These endpoints are collected for 16 weeks following randomization by review of VUMC's electronic medical record:

a) New, persistent, or recurrent infection: defined by positive culture and/or change in antibiotic regimen
b) Completion of antibiotic therapy
c) Days from negative blood culture (i.e., blood draw date) to first hospital discharge

Implementation Endpoints

a) Acceptance of Bridge Clinic as a bridging provider, defined by being physically checked in for at least 1 visit with the Bridge Clinic within 16 weeks of follow up.
b) Reasons for ineligibility among participants screened, specifically:
    - Absence of a qualifying OUD
    - Previously linked with a MOUD provider either prior to or during the current visit?
    - ACT determines the participant does not qualify

Fidelity Endpoint

a) Cross-over, defined as when a patient randomized to usual care is offered the Bridge Clinic, or when a patient is randomized to Bridge Clinic but is only offered usual care, at the time of discharge from the inpatient stay.

Analysis dataset
The analysis for the trial will use an intent-to-treat approach to answer the effectiveness question posed. That is, participants will be evaluated by treatment group as assigned regardless of what was delivered. All eligible participants will be included. There is no plan to restrict the analysis to a per protocol set.

Statistical Approach
Our initial analysis will be descriptive in nature, summarizing information that characterizes the cohort and the outcomes. Then, we will proceed with inferential analysis to answer the main study question. Then, we will compare the secondary endpoints between study groups.

Descriptive Analysis
To characterize the study sample, baseline demographic and clinical data will be described overall and by group. Categorical variables will be described using frequencies and proportions, and continuous variables will be described using means and standard deviations, as well as medians and interquartile ranges. Missingness will be reported for each variable. Graphical summaries using box plots, violin plots, and/or histograms may be used to describe the data graphically. At a minimum, the following variables will be described at time of enrollment:

- Age (years)
- Gender (male, female, unknown)
- Race (African American, Asian/Pacific Islander, Caucasian, Multiple, Native American, Other, Unknown)
- Ethnicity (Hispanic, Non-Hispanic, Unknown)
- Census tract area deprivation index

We will describe all of the outcome variables overall and grouped by study arm using the same approach as for the demographic data. Summary statistics and graphical representations may be displayed, and missingness will be reported for each variable.

No statistical comparisons between groups will be done for this descriptive analysis.

Main Analysis
The primary outcome variable (hospital index length of stay) will be compared between groups using an adjusted generalized linear model. Since the data are positive and may be skewed, like a gamma distribution, we may use a negative inverse link function, a proportional odds model, or transform the data.

In this analysis, group assignment is the main predictor variable. For drawing conclusions about the effect of the Bridge clinic, a critical p-value of 0.05 for the effect of treatment group assignment on the primary outcome will be used. The model will be adjusted for age, race, ethnicity, and area deprivation index. The influence of continuous variables will be assessed using restricted cubic splines with a minimum of three knots. We do not expect missingness in our primary outcome. If there are missing covariates, cases will not be excluded; we will use multiple imputation with predictive mean matching for missingness in adjusting covariates.

Secondary and implementation outcomes will be compared between study groups using adjusted generalized linear models, just as for the primary endpoint. Binary endpoints will use a logit link function. For counts, such as number of medication refills, either a zero-inflated Poisson or a negative binomial model will be fit.

Exploratory outcomes for OPAT patients will not be compared between study groups but will be reported by study group.

There may be missingness in secondary or implementation outcomes. If there are missing outcomes, these may be imputed of they occur in less than 5% of cases. Otherwise, the cohort for which the outcome is available will be described, along with the results of the model evaluating treatment effects in this cohort. All model results will be summarized with point estimates and 95% confidence intervals (CIs), which will be emphasized over p-values when reporting the results for secondary and implementation outcomes. No adjustments for multiplicity will be made.

Differential treatment effects
To determine whether effects of treatment on the primary endpoint depends on any of the baseline characteristics, we will test the interaction between the baseline characteristics and treatment effect in the regression model. If evidence of an interaction is observed using a threshold of $p<0.2$, we will proceed to subgroup analyses. For categorical variables, endpoints will be compared between within categories. For continuous variables, we will display the partial effects plots showing how treatment effects change with the putative subgrouping variable.

Summary

The results of this study will help to determine whether the Bridge Clinic is effective at improving patient outcomes. The analysis approach we describe is selected based on the trial's pragmatic nature and the intent to understand the effectiveness of Bridge Clinic when compared to TAU.