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

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1.0 Study Summary

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

Study Aims:

- Aim 1: To determine whether referral to the Bridge Clinic reduces overall index hospital length of stay when compared to direct referral to a long-term outpatient addiction provider for patients with active opioid use disorder (OUD) being considered for medications-for-addiction treatment (MAT).
- Aim 2: To evaluate the effects of the same intervention in the same population on secondary outcomes including costs, care-linkage, readmission rates, self-reported buprenorphine or naltrexone fills, rate of known recurrent opioid use, and measures of overall quality of life.
- Aim 3: Evaluate fidelity outcomes including Bridge Clinic acceptance and attendance rates among those referred to Bridge Clinic and reasons why patients were not considered to be eligible for inclusion.
- Aim 4: Among the subgroup of patients with an infection for which a course of IV antibiotics is required, additionally evaluate whether access to the Bridge Clinic facilitates outpatient management of the antibiotic therapy, with consequent improvement in clinical (infection and mortality) and resource (inpatient days, time to discharge following a negative blood culture) outcomes.

Study Hypotheses:

- Primary: Among patients with active OUD being considered for MAT, index hospital length of stay will be shorter among patients randomized to referral to the Bridge Clinic than among patients randomized to no referral to the Bridge Clinic.
- Secondary: Among patients with active OUD being considered for MAT, total costs, readmission rates, and rate of recurrent opioid use will be lower while successful care-linkage, self-reported buprenorphine or naltrexone prescription fill rates and quality of life will be higher among patients randomized to referral to the Bridge Clinic than among patients randomized to no referral to the Bridge Clinic.
- Exploratory: Among patients with active OUD being considered for MAT who also have an infection requiring IV antibiotics, referral to the Bridge Clinic will result in lower resource use without worse clinical outcomes when compared with not being referred to the Bridge clinic.

Study Population: Inpatients with OUD being considered for medications-for-addiction treatment (MAT) who have not previously utilized Bridge Clinic.

Due to COVID and the resulting changes in patient flow, we will temporarily suspend eligibility for the trial for OPAT patients as of December 3rd, 2020.

Comparators:

- Direct referral to a long-term outpatient addiction provider
- Referral to the Bridge Clinic while long-term outpatient addiction provider is located/identified

Randomization: Randomization will occur at the individual patient level. Currently, the Bridge Clinic can only accept a limited number of patients. To learn from the care provided, we propose randomizing all patients eligible for referral to Bridge Clinic in a ratio such that the Bridge Clinic is at capacity. In this way, the choice to refer is unbiased and the strength of evidence is greatly enhanced.

Consent: This study involves comparing two approaches to care: i) inpatient MAT (buprenorphine or naltrexone) with search for an outpatient MAT provider to accept the patient, or ii) inpatient MAT (buprenorphine or naltrexone) with referral to the Bridge Clinic to maintain the patient's care until a long-term outpatient MAT provider accepts the patient. Both approaches represent standard of care.

It is not practicable to answer the research question with informed consent because patients who choose to participate will necessarily differ from those who do not in substantial ways, including access to care.

We request a waiver of consent as 1) all data for the research will be obtained from the medical record, financial systems, state-mandated reporting systems, and from routine standard of care telephonic outreach to patients, 2) we are comparing usual care practices, albeit with randomization, 3) there is no additional interaction with the participant for research purposes, and 4) it is impracticable to conduct the research with consent.

2.0 Background

Opioid overdoses continued to increase in Tennessee in 2017, where rates of overdose already exceed the national average, and these trends were reflected in VUH admissions for opioid use disorder (OUD)-related problems, which were up 55% in the first 6 months of 2018 over 2017.[1] Vanderbilt is implementing several initiatives to improve outcomes in patients with OUD. On July 20th, 2018, a new Addiction Consult Team (ACT) went live at Vanderbilt. The service has completed 1,082 patient visits as of May 29th 2019 (373 new visits and 709 follow up visits). Additionally, we have created an outpatient "Bridge Clinic" at VUMC that is available to manage patients with OUD for a transitional period of up to 3 months following hospital discharge. ACT clinicians staff both the consult service and the Bridge Clinic, providing continuity of care to patients leaving VUH. Staff include internal medicine, psychiatry, pain-anesthesia, nursing, social work and a recovery coach. A patient discharged from VUH who is deemed appropriate

[1] https://www.drugabuse.gov/drugs-abuse/opioids/opioid-summaries-by-state/tennessee-opioid-summary. Last accessed 11/5/18.

for the Bridge Clinic is written a bridge script for buprenorphine MAT. Upon discharge and between Bridge Clinic visits, the use of VUMC preferred communications (telephone, text, email) outreach by case management is implemented; telephone outreach may improve outcomes similarly to face-to-face contact among addicted patients.[2]

The Bridge Clinic was designed and implemented based on work completed at MGH, Boston Medical Center, Yale and UAB. The intent is to obviate the challenge that patients being considered for MAT are often not discharged until an outpatient provider willing to accept the patient has been identified, resulting in delays to discharge. By serving as a bridging provider, any delay in discharge is avoided. Moreover, the subset of patients requiring IV antibiotic therapy are often admitted for a full six-week course of treatment unless a skilled nursing facility is available, also at considerable expense to the healthcare system. For patients meeting low risk criteria, the multi-specialty Bridge Clinic is available to manage the antibiotic therapy as an outpatient. This provides further opportunities for the Bridge Clinic to broadly impact the hospital bed days dedicated to caring for this patient population while simultaneously providing access to dedicated care. While implemented clinically based on available evidence, the effectiveness of this care model in improving patient outcomes while reducing time in hospital has yet to be quantified in situ.

3.0 Rationale and Specific Aims

In order to rigorously evaluate the impact of the Bridge Clinic on improving care for patients with OUD, a randomized controlled trial is needed. Evidence generated in this way will support either the sustained implementation of the Bridge Clinic with scale up to meet demand, or sufficient evidence will accumulate to indicate the expected impact is not achieved and alternative approaches are needed to improve the system of care for OUD patients being considered for MAT. Given the overarching goal of evaluating the Bridge Clinic as it is operating, the specific aims of this study are to:

- Aim 1: To determine whether referral to the Bridge Clinic reduces overall index hospital length of stay when compared to direct referral to a long-term outpatient addiction provider for patients with active opioid use disorder (OUD) being considered for medications-for-addiction treatment (MAT).
- Aim 2: To evaluate the effects of the same intervention in the same population on secondary outcomes including costs, care-linkage, readmission rates, self-reported buprenorphine or naltrexone fills, rate of known recurrent opiate use, and measures of overall quality of life.

[2]McKay, J. R., Lynch, K. G., Shepard, D. S., & Pettinati, H. M. (2005). The effectiveness of telephone-based continuing care for alcohol and cocaine dependence: 24-month outcomes. *Archives of general psychiatry*, *62*(2), 199-207. McKellar, J., Wagner, T., Harris, A., Oehlert, M., Buckley, S., & Moos, R. (2012). One-year outcomes of telephone case monitoring for patients with substance use disorder. *Addictive behaviors*, *37*(10), 1069-1074.

- Aim 3: Evaluate fidelity outcomes including Bridge Clinic acceptance and attendance rates among those referred to Bridge Clinic and reasons why patients were not considered to eligible for inclusion.
- Aim 4: Among the subgroup of patients with an infection for which a course of IV antibiotics is required, additionally evaluate whether access to the Bridge Clinic facilitates outpatient management of the antibiotic therapy, with consequent improvement in clinical (infection and mortality) and resource (inpatient days, time to discharge following a negative blood culture) outcomes.

To complete these aims, patients admitted to VUH with OUD and being considered for MAT, who have not previously utilized Bridge Clinic, will be enrolled in a pragmatic, single-center, randomized, controlled trial comparing referral to Bridge Clinic versus no referral to usual care in the community. Randomization ratio will be set to ensure the Bridge Clinic is functioning at capacity and the remaining patients will serve as the control. For example, if there is an average of five available slots for new referrals to the Bridge Clinic in a week, and there is an average of 20 eligible patient discharges in a week, the randomization ration will be set as 1:3.

If the Bridge Clinic is successful in bridging buprenorphine-naloxone use (as well as IM naltrexone in some cases) and linking to additional care, it is expected to decrease the overall length of stay of patients with OUD who are initiating buprenorphine-naloxone therapy. This reduction in length of stay for these patients will reduce costs and increases bed availability for other patients while simultaneously providing these patients with the care they need.

4.0 Inclusion/Exclusion Criteria

Inclusion Criteria:

- Inpatients at VUH with active OUD being considered for MAT who have not previously utilized Bridge Clinic
- Patient accepting a transitional prescription for buprenorphine-naloxone or IM naltrexone whose outpatient plans are not fixed

Exclusion Criteria:

- Deemed ineligible for referral to outpatient Bridge Clinic by the ACT (examples include by are not limited to patients with severe, active co-occurring psychiatric disorders requiring a higher level of psychiatric care or patients for whom methadone maintenance is deemed the best choice of MAT).
- Patients previously randomized in this study.
- Patients previously utilized Bridge Clinic

5.0 Enrollment/Randomization

The Addiction Consult Team (ACT) will be notified of potentially eligible patients via an EPIC consult order or referral from the general or homeless psychiatry service. Those patients for whom an order for an addiction medicine consultation is placed will be evaluated by the ACT for MAT. If the ACT considers MAT to be clinically appropriate, the patient does not have set plans for outpatient care, and the patient has not been previously randomized in this study, they will be enrolled and randomized. All other patients will be treated with usual care without availability of referral to the Bridge Clinic.

Screening information from enrolled patients will be entered into REDCap. For patients meeting objective criteria but whom the ACT determine ineligible for MAT, the reason for not enrolling them will be collected.

Once eligibility is confirmed, the patient will be randomized to being offered referral to the Bridge Clinic or not, as described below. Randomization will occur at the individual patient level. Randomization ratio will start at 1:1 and will be updated as necessary, but no more frequently than bi-weekly, to maintain the Bridge Clinic at capacity.

6.0 Study Procedures

An enrolled patient will receive a referral to social work for "outpatient MAT". The ACT social worker will approach the patients with resources for outpatient MAT determined by randomization (though the social worker can escalate patients in either condition to a higher level of care as appropriate after randomization). All patients will be offered usual information about outpatient MAT. Patients randomized to be eligible for referral to the Bridge Clinic will additionally receive information about the Bridge Clinic and this will be offered as an option during discussion of the plan for MAT. Patients who are randomized to not being offered a Bridge Clinic referral will not receive information about the Bridge Clinic and the Bridge Clinic will not be offered as an option.

Subsequent to comparator group assignment, patients will be followed to measure outcomes. All data will be captured from the medical record, financial systems, state-mandated reporting systems, and from other standard of care documentation. The data elements to be collected include the following:

<u>Baseline demographics collected at time of enrollment</u>

- Age
- Gender
- Race
- Ethnicity
- SES indicators

<u>Primary Endpoint</u>

- Overall index hospital length of stay

Additional Endpoints collected for 16 weeks following randomization

- Costs of care (total costs, and costs for each admission and care resource used (e.g. Bridge Clinic))
- Linkage to MAT provider (attending at least one visit with a MAT provider)
- Self-reported buprenorphine-naloxone (or naltrexone) prescriptions filled
- Readmission
- ED visits
- Hospital and ED free days
- Recurrent opiate use
- Overall quality of life as measured by the Schwartz Outcome Scale-10 (SOS10)
- Overdose
- Death
- Cross-over to Bridge Clinic to community care or vice-versa

Additional Endpoints for patients with infection suitable for outpatient management, collected for 16 weeks following randomization

- New, persistent, or recurrent infection (as defined by a positive culture and/or change in antibiotic regimen)
- Completion of antibiotic therapy
- Days from negative blood culture to first hospital discharge

Implementation Measurements

- Acceptance of Bridge Clinic as a bridging provider
- Reasons for ineligibility

Data will be abstracted from the EMR, REDCap and the Research Derivative (RD). The Research Derivative is a database of clinical and related data derived from the Medical Center's clinical systems and restructured for research. Data is repurposed from VU's enterprise data warehouse, which includes data from StarPanel, VPIMS, and ORMIS (Operating Room Management Information System), EPIC, Medipac, and HEO among others. The medical record number and other person identifiers are preserved within the database. Data types include reimbursement codes, clinical notes and documentation, nursing records, medication data, laboratory data, encounter and visit data, among others. Output may include structured data points, such as ICD 9 codes or encounter dates, semi-structured data such as laboratory tests and results, or unstructured data such as physician progress reports. The database is maintained by the Office of Research Informatics under the direction of Paul Harris, Ph.D.

7.0 Risks and Benefits

The risks associated with this study are limited to those associated with protection of private health information; beyond the randomization, the interaction with human subjects is limited to collection of data from existing records. Allocation made by randomization is between two usual approaches of care: i) inpatient MAT

(buprenorphine or naltrexone) or appropriate alternative until a long-term outpatient MAT provider accepts the patient (sometimes after SNF stay), or ii) inpatient MAT (buprenorphine or naltrexone) or appropriate alternative with referral to the Bridge Clinic, who will maintain the patient's care until a long-term outpatient MAT provider accepts the patient. Currently, the Bridge Clinic can only accept a limited number of patients and so the choice of approach is based on availability. By randomizing the availability of the Bridge Clinic, it is possible to derive knowledge of the impact of the clinic on patient outcomes that would otherwise not be discoverable without bias. The results of this study will help understand the impact of the Bridge Clinic and be used as data for potentially expanding the resources and availability of the Bridge Clinic to additional patients or refining services to improve patient care.

We expect that patients randomized to being eligible for Bridge Clinic services will experience decreased overall length of stay. We also expect overall reduced costs. The resource savings benefit not only the study participant, but this approach will open up hospital days/beds for other patients.

Risks associated with the collection of personal health information (PHI) will be mitigated by taking all reasonable efforts to keep the information private and confidential. The minimum amount of health information necessary for study conduct will be abstracted from the medical record. PHI will be entered into REDCap, which is a secure platform for maintaining research data. Identifiers will be needed to prevent duplicate enrollments and to track patients through the health system, but user level access will be set up to limit access to any identifiers only to those study personnel who need this access. Analysis datasets may be stored on secure servers but will not include direct identifiers. Direct identifiers will not be included in datasets unless absolutely necessary.

8.0 Reporting of Adverse Events or Unanticipated Problems Involving Risk to Participants or Others

Participating in the study does not add risk related to treatment. The Bridge Clinic is operational and provides usual clinical care to those patients fitting within its capacity. All other processes for linking patients to outpatient MAT are well established. Events associated with MAT or other care of patients are clinical and not associated with the research. Risks to patients from participating in the study are limited to the collection of PHI. We recognize there may be adverse events related to loss of privacy. These will be reported according to appropriate timelines. The Principal Investigator will be responsible for overseeing the study on a daily basis.

9.0 Study Withdrawal/Discontinuation

Because this study involves only observational data collection after randomization to Bridge Clinic or no Bridge Clinic availability, there are no plans to withdraw participants

or discontinue them in the study. Implementation outcomes, such as uptake of Bridge Clinic referrals, are important to gather and will be included. If a patient requests that their records not be included in any research, they will not be included and all data collected for this study will be removed from the dataset. However, if analyses have already been completed and reported at the time of the request, we will retain a copy of the data in a de-identified manner to ensure rigor and reproducibility of the research.

10.0 Statistical Considerations

Statistical Analysis Plan:
Initially, we will characterize participants overall and grouped by study arm using descriptive statistics (e.g. means with standard deviations, medians with interquartile range, and counts with percentages, as appropriate). Data may also be described graphically. The primary analysis will compare length of index hospital stay between those offered referral to the Bridge Clinic and those not offered referral to the Bridge Clinic on an intent-to-treat basis. We will compare length of stay using a generalized linear model with group assignment as the primary predictor variable, with adjustment for important covariates. We expect to model the outcome as a continuous outcome. We may choose to use a proportional hazards model or a gamma GLM with a log-link function if the data are substantially skewed; we do not expect this based on our experience with length of stay in this patient cohort. For secondary outcomes, costs will be similarly modeled. Binary outcomes will be modeled using logistic regression, Quality of life outcomes will be modeled using a proportional odds regression. Additional analyses that we expect to perform include 'per protocol' comparisons between study groups and characterization of implementation measures.

Power and Sample Size Considerations:
We estimate 700 patients per year, or about 14 patients per week, will be eligible to participate in this study, with a capacity for approximately 3-4 new patients per week to be seen at the Bridge Clinic. We expect approximately 2/3 of patients referred to the Bridge Clinic to make their first appointment. Therefore, we will randomize patients at a rate of 1:1 to Bridge Clinic versus usual care. The randomization may be adapted if eligibility and follow up rates are different to expected. The mean length of stay for patients is currently 15 days, ranging from 3-42 and a standard deviation of about 15 days. With 700 patients in a year, allocated 1:1, we will have about 80% power to detect a 3-day reduction in length of stay. This does assume a reduced standard deviation of 10 days. If the standard deviation remains at about 15 days, the difference detectable with 80% power is 3.5 days.

Interim Analysis
Because of the disruption caused by COVID-19 and lower than expected enrollment, midway through the recruitment period we decided to re-estimate the sample size based on the experience of patients. Blinded to allocation, we estimated the distribution of length of stay for all enrolled patients. We found the mean length of stay was shorter, at 9 days, with a standard deviation of 11. However, the distribution was decidedly right

skewed. Therefore, we log transformed the length of stay variable for deciding on the final sample size. The mean length of stay was ln(5.5) days with a standard deviation of ln(2.7) days. **Assuming that a reduction in length of stay of 1.5 days is meaningful and the observed common standard deviation is a good estimate, about 168 patients per group, or 336 patients total, would be required to have 80% power to detect a difference**.

11.0 Privacy/Confidentiality Issues

At no time during the course of this study, its analysis, or its publication will patient identities be revealed. The minimum necessary data will be collected and data containing patient or provider identifiers will only be obtained as required to complete the research. Data will be unlinked from identifiers, using a unique key to facilitate linkage when needed. Data will be collected into a password-protected, secure, web-based application for managing research data (REDCap). All patients will be assigned a unique study number for use in the computerized database. At the time of publication all identifiers will be removed from the archival dataset.

12.0 Follow-up and Record Retention

The initial study is anticipated to progress from initiation to completion in about 12 months. For each participant, the study will commence at enrollment and last until 16 weeks from randomization. Patient clinical outcomes will be collected. Identified data in the secure database will be stored consistent with record retention requirements, typically 5 years from completion of the research. De-identified dataset will be maintained for secondary analyses and to support the reproducibility of reports.