Summer 6-16-2023

Linkage to Outpatient Treatment in Inpatients with Alcohol Use Disorder Started on Naltrexone

Stephanie Stamatis

LINKAGE TO OUTPATIENT TREATMENT IN INPATIENTS WITH ALCOHOL USE DISORDER STARTED ON NALTREXONE

A Thesis Presented to

The Faculty of the School of Medicine

Yale University

In Candidacy for the Degree of

Master of Medical Science

June 2023

Stephanie Stamatis, PA-S

Class of 2023

Yale Physician Associate Program

Srinivas Muvvala, MD, MPH

Associate Professor of Psychiatry

Yale School of Medicine

Table of Contents

List of Graphs

List of Tables

Abstract

Naltrexone is a full opioid antagonist approved for the treatment of alcohol use disorder that can effectively reduce alcohol consumption. There are few studies that study the impact of starting naltrexone for alcohol use disorder in the inpatient setting. We propose to compare rates of outpatient treatment follow-up for alcohol use disorder in hospitalized patients who are referred to treatment without initiating naltrexone versus those initiated on oral naltrexone or injectable naltrexone. Using an open-label, randomized clinical trial design, we will enroll 75 adults aged 18 to 55 with alcohol use disorder admitted to a general medicine inpatient service and track their follow-up with outpatient treatment. This study will provide insight on the impact of initiating naltrexone for alcohol use disorder in the inpatient setting and on linkage to outpatient care.

Abbreviations

AUD – Alcohol Use Disorder

AUDIT-C – Alcohol Use Disorders Identification Test-Concise

IRB – Institutional Review Board

MAUD – Medications for Alcohol Use Disorder

MAT – Medication-assisted Treatment

SBIRT – Screening, Brief Intervention and Referral to Treatment

Chapter 1: Introduction

1.1 Background

Alcohol use in the United States is common with around 138.3 million people actively using alcohol. Around 15.7 million Americans meet criteria for an alcohol use disorder (AUD)[1,2]. Unhealthy alcohol use continues to be a public health concern due to the short- and long-term health consequences associated with it. Excessive alcohol use, referring to binge drinking, heavy drinking, and drinking by a person who is pregnant or less than 21 years of age, is of particular concern. Excessive alcohol use can increase the risk of injury, motor vehicle crashes, unintended pregnancy, sexually transmitted infections, and poor pregnancy outcomes. It is also associated with chronic diseases including cardiomyopathy, high blood pressure, stroke, liver disease, and cancer[3]. In the United States alone, excessive alcohol use is responsible for around 95,000 deaths each year[4]. Beyond physical health concerns, AUD can affect a person's employment status, interpersonal relationships, socioeconomic status, and contribute to legal issues, underscoring the urgency of its treatment. AUD is a chronic illness that can cause a variety of health, social, and economic issues both on the individual and community level.

Understanding effective strategies to address unhealthy alcohol use has become more pressing in recent years as the COVID-19 pandemic has affected how Americans drink. There have been increases in drinking among women,[5] African Americans, and an increase in AUD among those aged 35-49[6]. These drinking pattern changes in the United States emphasize the importance of researching AUD in all genders and race/ethnicities as AUD becomes more prevalent across different demographic groups. This also brings attention to AUD among younger adults who may benefit from reducing alcohol consumption to prevent negative health

outcomes[7,8]. As the population affected by unhealthy alcohol consumption continues to widen, new approaches are required to effectively intervene.

One evidence-based intervention strategy used is Screening, Brief Intervention and Referral to Treatment (SBIRT). SBIRT is an effective approach used to identify and intervene in patients who may be at risk of a substance use disorder including AUD. This intervention was developed to detect AUD using validated screening methods such as the Alcohol Use Disorders Identification Test-Concise (AUDIT-C) and intervene in unhealthy alcohol use using motivational interviewing followed by a referral to treatment if warranted. In a systematic review of SBIRT in the emergency department setting, the brief intervention and motivational interviewing has shown to have short-term, but not long-term, effectiveness in reducing at-risk drinking[9]. While this intervention can improve detection and help reduce some negative consequences of alcohol use, there is still a need to do more to intervene in patients with unhealthy alcohol use, particularly AUD.

In addition to behavioral interventions used for the AUD management, there are medications available for patients that show promising results in reducing alcohol intake[7,10]. The Food and Drug Administration (FDA) has approved medications for AUD treatment including naltrexone, acamprosate, and disulfiram. Naltrexone is a medication approved for the treatment of both AUD and opioid use disorder (OUD). Naltrexone works to reduce cravings and alcohol consumption by preventing the euphoric effects associated with drinking[11] and is available in both intramuscular and oral formulations. Acamprosate is an oral medication with an agonistic effect at $GABA_A$ receptors and a weak antagonistic effect at both N-methyl-D-aspartate receptors and metabotropic glutamate receptor 5 though the mechanism of action in AUD is not fully understood. Acamprosate has been found effective in achieving alcohol abstinence[12]. Disulfiram

is another MAUD that blocks aldehyde dehydrogenase 2, the enzyme responsible for metabolizing alcohol to acetaldehyde, leading to nausea, vomiting, headaches, flushing, sweating, and palpitations following alcohol consumption[10,12]. It is no longer a first-line treatment and recommended to be used only for abstinence in a supervised environment due to the adverse effects[12]. Other pharmacotherapy options that are not FDA approved include baclofen, gabapentin, topiramate, and nalmefene[10].

The FDA-approved medications are effective with low numbers needed to treat (NNT), or the number of patients needed to treat to prevent one adverse outcome, seen in naltrexone and acamprosate. The NNT for naltrexone for reducing heavy drinking is 12 and abstinence is 20 while the NNT for acamprosate for reduced drinking is 9 and return to any drinking is 12, comparable to NNT for common medications including aspirin, antihypertensives, and antibiotics[12]. Despite how effective these medications can be in managing AUD, they are underutilized in healthcare. Of those who undergo treatment for AUD, less than 9% receive pharmacotherapy[10,12]. It is important to understand why these prescribing rates are low and what can be done to increase them.

Medications for alcohol use disorder (MAUD) can be chosen based on several factors including recovery goals. Abstinence has traditionally been the primary goal of alcohol recovery but even a reduction in alcohol intake can improve alcohol-related outcomes[7,10]. While acamprosate and disulfiram work better to achieve abstinence, naltrexone can help with alcohol use reduction. Naltrexone is a full mu-opioid antagonist available in both an oral and extended-release intramuscular formulation. Oral naltrexone is dosed once daily- and extended-release naltrexone is given intramuscularly every 4 weeks. The mechanism of action in OUD is that as a pure opioid antagonist, naltrexone completely blocks the subjective effects of opioids and blocks

the physical dependence to opioids[13]. The mechanism of action in AUD is less understood although preclinical data suggests the possible involvement of the endogenous opioid system[13,14]. According to a Cochrane review, naltrexone has been shown to reduce the amount and frequency of drinking when compared to a placebo[15]. Extended-release naltrexone may be given with the intention that the infrequent dosing schedule may improve medication adherence and treatment retention compared to the daily dosing required of the oral formulation. While there are a few smaller studies that compare the two formulations, there are no large studies that directly compare the efficacy of these two formulations[12] or provide evidence for increased medication adherence.

Additionally, there are a few studies that examine inpatient discharge and linkage to outpatient treatment for AUD. Trowbridge et al studied the addition of an inpatient consult service and showed improvement in diagnosing, treating, and linking patients to outpatient services primarily for opioid use disorder and AUD. They also found initiating medications for AUD and opioid use disorder feasible in the inpatient setting with 33% of patients prescribed naltrexone for AUD exclusively attending their post-discharge visit[16]. Beauchamp et al similarly found the medication-assisted treatment (MAT) implementation in the emergency and hospital setting to be feasible although the study was limited in its ability to assess the effectiveness of linking patients to outpatient services[17]. These studies have shown the feasibility of initiating treatment for substance use disorder in the inpatient setting, but more research is required to show the effect on outpatient follow-up and linkage to services following discharge.

Naltrexone and other approved MAUD have primarily been studied in the outpatient setting. Recent studies have estimated 15-16% of hospitalized patients have an active substance use disorder[16,18]. The inpatient setting provides an opportunity to identify and intervene in AUD for

patients who may not regularly engage in outpatient healthcare services. There are few studies examine medication initiation for AUD in the inpatient setting. Studies that have been completed in the inpatient or emergency department setting are primarily feasibility studies[17,19-21], focus on veteran populations[21-24], or measure readmission rates[24,25]. There is a need to study initiating naltrexone in the inpatient setting and how this affects outpatient treatment for AUD. This is an important unanswered question, as starting medication is an initial step in effectively managing AUD.

1.2 Statement of the Problem

While there are effective FDA-approved medications for alcohol use disorder available, they are underutilized in both inpatient and outpatient settings. This may be due to multiple factors including patient education, provider education and comfortability in prescribing MAUD, insurance coverage, out-of-pocket costs, and access to outpatient treatment services. In addition, there are studies that focus on the outpatient setting as a place for intervention and treatment of AUD. For those who do not have a primary care provider or regularly use outpatient healthcare services, hospitalization provides another opportunity for intervention.

Previous studies have shown promising results for intervening in patients with AUD in the inpatient setting. While there are recent studies that look at initiating MAUD in the inpatient setting, they are either feasibility studies, focused on veteran populations, or measure the risk of readmission as their primary outcome. Other outcomes that are important to study may include the effect of the medication on other clinical outcomes including medication adherence, reduction in drinking, and outpatient treatment follow-up. There is an overall need to study how initiating naltrexone and other MAUD in the inpatient setting may affect connecting hospitalized patients to outpatient treatment. It is also important to compare extended-release and oral

naltrexone formulations directly with the control group to see if either formulation has better outcomes in this population.

1.3 Goals and Objectives

The goal of this study is to test the efficacy of initiating naltrexone for the treatment of AUD in hospitalized patients to help connect patients to outpatient treatment follow-up. This is important to study as the inpatient setting provides another opportunity for healthcare providers to address AUD, especially for those patients who may not utilize outpatient healthcare services regularly. The primary objective of this study is to compare follow-up rates of outpatient treatment for AUD in patients who are referred to outpatient treatment in the inpatient setting without initiating naltrexone versus those initiated on oral naltrexone or extended-release naltrexone. There are two secondary objectives planned for this study. The first secondary objective is adherence to either oral or extended-release naltrexone after 4 weeks, 6 weeks, and 12 weeks assessed by medication dispense history or documentation of injection, respectively. The second secondary objective for this study is the change in percentage of heavy drinking days per week based on participant self-reporting at the defined study points. Heavy drinking days are defined as 5 or more drinks per day for men and 4 or more drinks per day for women.

1.4 Hypothesis

We hypothesize that there will be a difference in the proportion of linkage to outpatient treatment of hospitalized patients with AUD within 12 weeks of discharge between patients prescribed extended-release naltrexone before discharge plus referral to treatment, patients prescribed oral naltrexone before discharge plus referral to treatment, and patients referred to treatment without medication initiation. Linkage to outpatient treatment is defined as attendance to at least one outpatient follow-up visit for the treatment of AUD. Our alternative hypothesis is

that there will not be a difference in the proportion of linkage to outpatient treatment of hospitalized patients with AUD within 12 weeks of discharge between patients prescribed extended-release naltrexone before discharge plus referral to treatment, patients prescribed oral naltrexone before discharge plus referral to treatment, and patients referred to treatment without initiating naltrexone.

1.5 References

1. Nehring SM, Freeman AM. Alcohol Use Disorder. StatPearls. 2022.

2. Quality CfBHa. Key substance use and mental health indicators in the United States: Results from the 2015 National Survey on Drug Use and Health. Vol. HHS Publication No. SMA 16-4984, NSDUH Series H-51. 2016. http://www.samhsa.gov/data

3. National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP). Excessive Alcohol Use. July 11, 2022. https://www.cdc.gov/chronicdisease/resources/publications/factsheets/alcohol.htm#print

4. Bohm MK, Liu Y, Esser MB, et al. Binge Drinking Among Adults, by Select Characteristics and State — United States, 2018. Vol. 70. 2021. Morbidity and Mortality Weekly Report.

5. Slade T, Chapman C, Swift W, Keyes K, Tonks Z, Teesson M. Birth cohort trends in the global epidemiology of alcohol use and alcohol-related harms in men and women: systematic review and metaregression. BMJ Open. Oct 24 2016;6(10):e011827. doi:10.1136/bmjopen-2016-011827

6. Kerr WC, Ye Y, Martinez P, et al. Longitudinal assessment of drinking changes during the pandemic: The 2021 COVID-19 follow-up study to the 2019 to 2020 National Alcohol Survey. Alcohol Clin Exp Res. Jun 2022;46(6):1050-1061. doi:10.1111/acer.14839

7. Witkiewitz K, Heather N, Falk DE, et al. World Health Organization risk drinking level reductions are associated with improved functioning and are sustained among patients with mild, moderate and severe alcohol dependence in clinical trials in the United States and United Kingdom. Addiction. Sep 2020;115(9):1668-1680. doi:10.1111/add.15011

8. Collaborators GBDA. Population-level risks of alcohol consumption by amount, geography, age, sex, and year: a systematic analysis for the Global Burden of Disease Study 2020. Lancet. Jul 16 2022;400(10347):185-235. doi:10.1016/S0140-6736(22)00847-9

9. Barata IA, Shandro JR, Montgomery M, et al. Effectiveness of SBIRT for Alcohol Use Disorders in the Emergency Department: A Systematic Review. West J Emerg Med. Oct 2017;18(6):1143-1152. doi:10.5811/westjem.2017.7.34373

10. Kranzler HR, Soyka M. Diagnosis and Pharmacotherapy of Alcohol Use Disorder: A Review. JAMA. Aug 28 2018;320(8):815-824. doi:10.1001/jama.2018.11406

11. Miller PM, Book SW, Stewart SH. Medical treatment of alcohol dependence: a systematic review. Int J Psychiatry Med. 2011;42(3):227-66. doi:10.2190/PM.42.3.b

12. Fairbanks J, Umbreit A, Kolla BP, et al. Evidence-Based Pharmacotherapies for Alcohol Use Disorder: Clinical Pearls. Review. Mayo Clin Proc. 2020;95(9):1964-1977. doi:10.1016/j.mayocp.2020.01.030

13. REVIA (naltrexone hydrochloride tablets USP) [package insert]. Pomona, New York: DURAMED PHARMACEUTICALS, INC. subsidiary of Barr Pharmaceuticals, Inc.; 2013.

14. VIVITROL (naltrexone for extended-release injectable suspension), for intramuscular use [package insert]. Waltham, MA: Alkermes, Inc.; 2022.

15. Rosner S, Hackl-Herrwerth A, Leucht S, Vecchi S, Srisurapanont M, Soyka M. Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev. Dec 8 2010;(12):CD001867. doi:10.1002/14651858.CD001867.pub3

16. Wakeman SE, Herman G, Wilens TE, Regan S. The prevalence of unhealthy alcohol and drug use among inpatients in a general hospital. Subst Abuse. 2020/07/02 2020;41(3):331-339. doi:10.1080/08897077.2019.1635961

17. Beauchamp GA, Laubach LT, Esposito SB, et al. Implementation of a Medication for Addiction Treatment (MAT) and Linkage Program by Leveraging Community Partnerships and Medical Toxicology Expertise. Article. J Med Toxicol. 2021;17(2):176-184. doi:10.1007/s13181-020-00813-4

18. Trowbridge P, Weinstein ZM, Kerensky T, et al. Addiction consultation services – Linking hospitalized patients to outpatient addiction treatment. Article. J Subst Abuse Treat. 2017;79:1-5. doi:10.1016/j.jsat.2017.05.007

19. Anderson ES, Chamberlin M, Zuluaga M, et al. Implementation of Oral and Extended-Release Naltrexone for the Treatment of Emergency Department Patients With Moderate to Severe Alcohol Use Disorder: Feasibility and Initial Outcomes. Ann Emerg Med. Dec 2021;78(6):752-758. doi:10.1016/j.annemergmed.2021.05.013

20. Azuar J, Questel F, Hispard E, Scott J, Vorspan F, Bellivier F. Hospital Stay and Engagement in Outpatient Follow-Up After Alcohol Emergency Detox: A 1-Year Comparison Study. Alcohol Clin Exp Res. Feb 2016;40(2):418-21. doi:10.1111/acer.12962

21. Busch AC, Denduluri M, Glass J, et al. Predischarge Injectable Versus Oral Naltrexone to Improve Postdischarge Treatment Engagement Among Hospitalized Veterans with Alcohol Use Disorder: A Randomized Pilot Proof-of-Concept Study. Comparative Study, Randomized Controlled Trial. Alcoholism: Clinical & Experimental Research. Jul 2017;41(7):1352-1360.

22. Leighty AE, Ansara ED. Treatment outcomes of long-acting injectable naltrexone versus oral naltrexone in alcohol use disorder in veterans. Ment Health Clin. Nov 2019;9(6):392-396. doi:10.9740/mhc.2019.11.392

23. Stewart H, Mitchell BG, Ayanga D, Walder A. Veteran adherence to oral versus injectable AUD medication treatment. Ment Health Clin. May 2021;11(3):194-199. doi:10.9740/mhc.2021.05.194

24. Beatty A, Stock C. Efficacy of long-acting, injectable versus oral naltrexone for preventing admissions for alcohol use disorder. Article. Ment Health Clin. 2017;7(3):106-110. doi:10.9740/mhc.2017.05.106

25. Wei J, Defries T, Lozada M, Young N, Huen W, Tulsky J. An inpatient treatment and discharge planning protocol for alcohol dependence: efficacy in reducing 30-day readmissions

and emergency department visits. J Gen Intern Med. Mar 2015;30(3):365-70. doi:10.1007/s11606-014-2968-9

Chapter 2: Review of the Literature

2.1 Introduction

A systematic review of the literature was conducted using multiple databases including PubMed, Scopus, OVID, Embase, and APA PsycINFO beginning in June 2022. A review of study design with a focus on randomized clinical trials was conducted simultaneously to review relevant methodology for the proposed study. The following search terms were used individually or in combination to find relevant literature: extended-release naltrexone, intramuscular naltrexone, injectable naltrexone, oral naltrexone, alcohol use disorder (AUD), alcohol, medication, medications for alcohol use disorder (MAUD), medication-assisted treatment (MAT), prescription, adherence, mean, mean difference, heavy drinking days, inpatient, hospitalized, hospitalization, CONSORT, clinical trial, and diagnostic and statistical manual of mental disorders. Results were filtered to find literature published within the past 20 years and with populations 18 years and older. Additional literature was found in references from the studies resulting from primary searches.

2.2 Review of Empirical Studies

2.2.1 Outpatient Setting

Most of the evidence available looks at MAUD use in an outpatient setting given the ability to conduct follow-up and opportunity for primary care providers to intervene. The Combined Pharmacotherapies and Behavioral Interventions, or COMBINE, is a 2004 study that examines the clinical outcomes of different medications used to treat AUD. This study included 16 different treatment groups in a randomized control trial to compare naltrexone, acamprosate, placebo, and no medication alongside different levels of behavioral counseling. The focus of this

study was to examine the effects of combining pharmacologic treatment of AUD with different behavioral interventions. This randomized control trial took place over three years with the active intervention lasting 16 weeks and follow-ups up to 68 weeks. Primary outcomes included the number of days participants abstained from alcohol through the end of treatment and the number of heavy drinking days during treatment. This study found that standard medical management and either naltrexone or combined behavioral intervention (CBI), but not naltrexone and CBI in combination, was associated with a significant difference in percent days abstinent (p-value = .009). In addition, naltrexone and CBI were associated with good clinical outcomes, defined as abstinence or moderate drinking without problems[1]. While this study has a large sample size and high internal validity[1], it is important to note the results are not very generalizable. Eleven sites in different geographical areas throughout the United States participated, allowing for a variety of patients to be involved. The study took place at academic centers rather than outpatient or primary care settings and the medication was provided to participants in blister packs. Although these conditions may have resulted in high medication adherence, it is hard to evaluate how insurance or other factors may impact a patient's ability to receive medication on their own.

Another study conducted in the outpatient setting focused on oral naltrexone versus placebo in a double-blind randomized control trial of young adults. Participants enrolled were aged 18-25 and reported more than 4 heavy drinking days in the past 4 weeks. Participants were randomized to naltrexone 25mg daily plus 25mg targeted or a daily matching placebo and followed for 8 weeks of treatment to measure the percentage of heavy drinking days and days abstinent. The study did not find a statistically significant difference between the treatment and placebo groups for the percentage of heavy drinking days (p-value = .58) or percent days

abstinent (p-value = .39)[2]. The study did find that the naltrexone group was associated with a decrease in drinking intensity (mean difference = -9.85; 95% CI, -19.33 to -0.37)[2], a secondary outcome defined by both the number of drinks per drinking day and percentage of drinking days with an estimated BAC ≥0.08 g/dL. This study focuses on a young adult population that is often neglected in AUD studies and provides information on college-age students. Limitations of the study include a short treatment and follow-up period and recruitment based on advertisements which may have only reached a limited study population. It will be important to follow patients for a longer period to help us understand the long-term clinical outcomes of naltrexone versus placebo.

Extended-release vs. oral naltrexone for alcohol dependence in primary care, or XON, is an open-label, randomized clinical trial that compares oral naltrexone and extended-release naltrexone in the primary care setting. Patients were recruited through in-clinic referrals or community recruitment and if eligible for study, randomized to oral naltrexone plus medical management or extended-release naltrexone plus medical management and followed for 24 weeks in active treatment and 52 weeks total in follow-up. The primary outcome was success or failure of Good Clinical Outcome, a dichotomous variable defined as two or fewer heavy drinking days during each 4-week block of the study starting at week 5. Primary outcome results have not been published yet, but there is promisingly high study visit retention with 171 participants completing the study, 24 in long-term follow-up, and 42 lost to follow-up[3]. This study is one of the first randomized clinical trials directly comparing oral versus extended-release naltrexone. Also, participants without insurance or on Medicaid are not excluded based on medical and psychiatric comorbidities[3] which may provide a more representative patient sample compared to other studies that exclude these participants.

2.2.2 Veteran Population

Clinical outcomes comparing oral and extended-release naltrexone have been previously studied in veteran populations. In a retrospective cohort study, the clinical outcomes of oral versus extended-release naltrexone were compared using healthcare utilization as the measure. The primary outcome of this study was alcohol-related hospital admissions within 90 days of starting naltrexone of which there was no statistically significant difference between the oral naltrexone and injectable naltrexone groups. There were differences seen in secondary outcomes: the oral naltrexone group had fewer alcohol-related admissions within 30 days of naltrexone initiation, 90-day ED visits, and 90-day clinic visits compared to the injectable naltrexone group[4]. Limitations of this study include small sample size, retrospective cohort, and nonrandomized design. There are also baseline factors that may have influenced healthcare utilization outside of the naltrexone formulation including health comorbidities, housing status, the severity of AUD, and the setting in which naltrexone was initiated.

Another retrospective cohort study was completed in 2019 to compare treatment outcomes of oral and extended-release naltrexone in a veteran population. Charts were reviewed for patients diagnosed with AUD who attended treatment as an outpatient with either oral naltrexone or extended-release naltrexone between August 2016 and July 2018. The primary outcome was time to relapse as defined by patient, family, or friend volunteered report, hospitalization for alcohol intoxication, positive ethyl glucuronide test, or elevated blood alcohol concentration level. Of the 49 eligible patients, median time to relapse for extended-release naltrexone was 150.5 days compared to 50.5 days in the oral naltrexone group (p-value = .01)[5]. While this study demonstrates better efficacy for extended-release naltrexone, it is important to note this is seen in a small sample size at a single site.

In Busch et al, a proof-of-concept study was conducted to compare oral and injectable naltrexone to assess feasibility. Veterans who were hospitalized and identified as having alcohol dependence by DSM-IV were randomized to receive a dose of oral naltrexone with a 30-day prescription or extended-release naltrexone with a second injection scheduled prior to discharge. These two groups were then followed to compare treatment initiation, engagement, and alcohol consumption for 45 days post-discharge. Treatment initiation and patients with ≥3 treatment visits within 30 days post-discharge did not differ significantly between groups[5]. It is important to note that this study was a feasibility study with a small sample size and without a control group for comparison.

2.2.3 Emergency and Inpatient Settings

The initiation of MAUD in settings outside of the outpatient setting provides another opportunity for treatment. A 2015 study looked at buprenorphine initiation for patients with opioid use disorder in the emergency setting. The study showed increased engagement in addiction treatment when patients were prescribed buprenorphine compared to those with brief intervention and referral alone (p-value < .001)[6]. Although the study is not specific to AUD, it provides an example of improving outpatient treatment engagement by intervening outside of a primary care setting. This may be especially helpful for patients who do not regularly engage in outpatient care or have frequent emergency department visits or hospitalizations due to substance use.

Despite the benefit of prescribing pharmacotherapy for substance use disorder outside of the primary care setting, there is little evidence that providers intervene in these settings. In a 2022 retrospective cohort study, encounters with an alcohol-related diagnosis were evaluated to measure MAUD prescribing in different care settings within a Colorado-based healthcare

system. Only 5% of the patients with an alcohol-related diagnosis were prescribed MAUD across all settings and were most likely prescribed in an inpatient substance use treatment setting. The odds ratio of being prescribed MAUD compared to inpatient substance use treatment was 0.8 (95% CI, 0.77-0.90) in a primary care setting, 0.13 (95% CI, 0.12-0.15) in the emergency setting, and 0.05 (95% CI, 0.041-0.060) in the inpatient setting[7]. Some limitations of the study include a retrospective cohort and exclusion of patients with a comorbid opioid use disorder. The study also did not determine whether patients were eligible for MAUD, only if patients were admitted with an alcohol-related diagnosis. The study included a large sample size and a variety of care settings throughout a single healthcare system. Overall, this study underscores the lack of intervention in settings outside of a specific inpatient substance use or primary care setting.

A 2021 study assessed the feasibility of implementing a program in the emergency department and inpatient setting that could be used to initiate medication-assisted treatment and connect patients to treatment for substance use disorder. This study focused on the addition of different team members that provided assessments and handoffs to the appropriate outpatient or specialized inpatient treatment center. Of the 1834 patients encountered during the 18-month study period, 298 linkages were performed by a group specifically for patients interested in MAT with 223 ultimately started on MAT[6]. Although this study did not focus on AUD solely and examined the feasibility of adding team members to facilitate treatment for substance use disorder, it demonstrates the utility of intervening in the emergency and inpatient settings.

Another study completed in the inpatient setting only examined the implementation process for counseling patients hospitalized for alcohol withdrawal and prescribed naltrexone before discharge. This pre-post study analysis followed patients for 30-day emergency department revisits and rehospitalizations both before and after the implementation of a program that

standardized discharge of patients with AUD including counseling on naltrexone. In the adjusted analysis comparing pre-intervention and post-intervention groups, the post-intervention group had lower 30-day emergency department revisit rates (OR = 0.47; 95% CI, 0.24-0.94) and rehospitalization rates (OR = 0.76; 95% CI, 0.30-1.92)[8]. It is important to note that the study had a smaller sample size, including the percentage of those in the postintervention group that were ultimately prescribed naltrexone. In addition, the percentage of comorbidities differed between the pre-and post-intervention groups. Overall, the study showed promise for clinicians in a general medicine inpatient setting routinely counseling and initiating naltrexone.

In a similar feasibility study, Terasaki et al looked at the effect of single-dose intravenous ketamine or intramuscular naltrexone in inpatients with AUD in reducing readmission rates. Participants were randomized to receive ketamine, naltrexone, or no treatment and all patients were linked to outpatient treatment. The study found that compared to the patients only linked to outpatient treatment, the ketamine and naltrexone arms had a lower relative risk, but the results were not statistically significant[9]. As with similar studies, the main outcome of this study was to determine the feasibility of starting MAUD in the inpatient setting and requires further study to provide evidence for clinical guidance. Other limitations of this study include a small sample size, unblinded design, and low follow-up rates[9]. Finally, despite being linked to outpatient treatment as an intervention, there was no data to assess the attendance of follow-up appointments to determine the effect either medication may have on outpatient treatment.

Several studies do try to assess follow-up to outpatient treatment from the inpatient or emergency setting. A 2021 descriptive feasibility study that looked at follow-up rates of patients with moderate to severe AUD prescribed oral or extended-release naltrexone in the emergency department. The analysis found that 15.3% of the 59 patients who received either formulation of

naltrexone attended follow-up within 30 days of discharge[7]. Although this study did not compare follow-up rates with a control group or between oral and extended-release naltrexone groups, it provides an example of how providers can intervene in AUD outside of the primary care setting.

Finally, Wei et al provide another example of a pre-post intervention study focused on implementing a discharge protocol for AUD including screening for naltrexone and arranging follow-up. This study also measured 30-day readmission rates and emergency department visits and found statistically significant differences between the pre-and post-intervention groups. The 30-day readmission rate was 23.4% in the pre-intervention group and 8.2% in the post-intervention group (p-value = .042), and ED visits occurred at a rate of 18.8% vs. 6.1% in the pre-and post-intervention groups respectively (p-value = .056)[10]. In addition, patients who were eligible for naltrexone in the pre-intervention group had a 38.5% readmission rate compared to those in the post-intervention group of 12.0% (p-value = .025) with only two out of three patients prescribed naltrexone in the post-intervention group[10]. It is limited by the study design and incomplete data as ED visits and readmissions outside of the study site were not included in measuring the primary outcome. This study is another example of a successful intervention for screening all patients who may be eligible for naltrexone in the inpatient setting but requires further study focused on patient outcomes.

2.3 Review of Relevant Methodology

2.3.1 Study Design

There is a need for randomized clinical trials to provide high-quality evidence in the clinical outcome assessment of oral and extended-release naltrexone in AUD[10]. There is a lack of randomized clinical trials that have been conducted, particularly outside of the outpatient setting[8]. Randomized clinical trials provide an effective way to assess the potential causal

relationship between an intervention and outcome[11,12]. In addition, the use of a randomized control trial will prevent bias that may be seen in a pre-post study analysis, descriptive studies, and retrospective observational studies. The Consolidated Standards of Reporting Trials, or CONSORT, guidelines and related literature were reviewed for the development of this randomized clinical trial.

2.3.2 Selection Criteria

Inclusion and exclusion criteria for this study are based on prior clinical trials[13] and the safety profiles of oral and extended-release naltrexone. The diagnosis of AUD will be made according to the DSM-V criteria for AUD[14] by the treating clinician. Participants must be currently hospitalized and at least 18 years old to 55 years old to capture an adult inpatient population. Eligible participants must be discharged into the community to accurately measure the primary outcome of connecting patients to treatment once discharged from the hospital.

Participants who are pregnant and/or breastfeeding are excluded from this study due to insufficient evidence for safety in pregnancy and breastfeeding[15,16]. Participants must be able to take oral medications as they may be randomized to the oral naltrexone group. Participants are not able to have had opioid-use with 10 days prior to study initiation based on extended-release naltrexone safety data[15] with current opioid use or a positive opioid urine toxicology screen based on previous studies[17] due to concern for induced opioid withdrawal. In addition, severe liver dysfunction, acute hepatitis, and increased liver function test levels are excluded due to the risk of hepatotoxicity associated with naltrexone[3,5,17]. Finally, participants with any uncontrolled significant physical or psychiatric illness that may preclude participants from adhering to treatment will be excluded from the study though future studies should be completed due to the prevalence of co-occurring psychiatric conditions and AUD[18].

2.3.3 Intervention

All participants will receive a referral to an outpatient clinic for the management of AUD. Social work and addiction medicine service can be involved to help the participant decide which clinic to follow up with based on location and preference. Participants in the oral naltrexone group will be given naltrexone at the recommended dose of 50mg PO daily[16]. Participants in the extended-release naltrexone group will be given naltrexone at the recommended dose of 380mg every 4 weeks delivered intramuscularly, alternating sites of injection at each administration[15]. Participants in the control group will not receive any MAUD before discharge from the hospital.

2.3.4 Potential Confounding Variables

There are many potential confounding variables found that affect clinical outcomes when studying naltrexone and AUD. Previous studies have found that social and demographic factors including age[19,20], gender[20], and housing status[9] have been noted as confounding factors. In their discussion, Stephens et al also discuss potential confounding factors including housing issues and the ability to afford medication[8] which may be linked to socioeconomic and insurance status, two other factors that may be important to consider. Azuar et al included social and familial support as a baseline characteristic in their study[21] which may also be a potential confounding variable in similar studies. Overall, it will be important to include sociodemographic information in the baseline assessment as these factors may influence the outcomes of this study.

Other potential confounding factors noted include comorbidities and the characteristics of AUD. Previous studies have also discussed how medical comorbidities and psychiatric comorbidities can be potential confounding factors[20,22]. PTSD has specifically been found to be a confounding variable in medication adherence for other medical conditions including HIV and hypertension[22]. In addition, certain aspects of AUD itself may be confounding. The severity of

AUD may affect clinical outcomes and act as a negative confounder in good clinical outcomes as the severity increases[22,23]. The number of years that a patient has had AUD and the presence of multiple substance use disorders are also potential confounding factors[20,22].

Another retrospective study specifically looked at patient and treatment characteristics and how this affected adherence to extended-release naltrexone in both AUD and opioid use disorder. They found medication adherence was associated with concurrent therapy whether it was residential, individual, group, or psychiatric therapy[24] which deviates from the findings of the COMBINE study[1]. The use of therapy outside of outpatient treatment will be important to note as a potential confounding variable.

2.3.5 Primary and Secondary Outcome Measures

Comparing the effects of oral versus extended-release naltrexone initiated in the inpatient setting requires patients to follow up and is imperative in comparing the two formulations. Azuar et al completed a prospective follow-up study that compared unscheduled and scheduled inpatient alcohol detoxifications with outcomes including length of hospital stay and engagement for a year following detoxification. Engagement was measured by attendance at the post-discharge with additional criteria including at least one follow-up visit attended and attending at least 5 outpatient visits in the year following discharge. They did not find a statistically significant difference between attendance in the emergency unscheduled detoxification group and the scheduled detoxification group[21]. Despite the small sample size and quasi-experimental design, the results suggest that despite not having a scheduled detoxification with outpatient preparation, patients who underwent emergency inpatient detoxification continued to follow up. Again, this highlights the importance of intervening in AUD in the inpatient setting and provides a measurable primary outcome to use in future studies.

Outpatient treatment follow-up is also examined in the Busch et al proof-of-concept study that compares oral and extended-release naltrexone in a veteran population. Prior to discharge, patients were randomized to receive either oral or extended-release naltrexone and followed for treatment engagement defined by at least 3 treatment visits in 30 days post-discharge or 2 or more visits per month in the 3 months following discharge. As a pilot study, there was not sufficient statistical power to compare the two groups[5] but the study provides another example of measuring outpatient treatment engagement for AUD.

Medication adherence is another important outcome to measure when comparing naltrexone formulations as the hope is that the use of extended-release naltrexone will improve adherence. This was confirmed in a retrospective chart review of patients at the VA who were started on a MAUD. The study compared medication adherence of extended-release naltrexone, oral naltrexone, acamprosate, and disulfiram and found higher adherence to extended-release naltrexone than oral naltrexone at multiple time points using the portion of days covered model[22]. In a similar study of medication adherence among a veteran population, Walker et al found statistically significant higher rates of adherence among both naltrexone formulations compared to disulfiram but not between oral and extended-release naltrexone[25].

Finally, previous studies have measured the number of drinks in a specified period to compare the effectiveness of different medications used to treat AUD[1,3,5,17,26-28]. Different iterations of this outcome include drinks per week, drinks per month, number of days abstinent, or number of heavy drinking days in a specified period. One double-blind randomized clinical trial compared oral naltrexone versus placebo in reducing alcohol consumption in young adults. Participants kept diaries of the number of drinks per day and used this data to compare the percentage of days abstinent and of heavy drinking days between each group[2]. Overall,

measuring alcohol consumption is an important outcome when comparing the effectiveness of different MAUD.

2.3.6 Sample Size and Statistical Analysis

Sample size will be calculated based on data from previous studies with similar outcome measures and will account for anticipated dropout rates. This will be calculated with a power (1 – β) of 80%, a type I error (α) of 5%, and an anticipated dropout rate of 20%. For the primary outcome, the percentage of participants in each group who attend outpatient treatment for AUD following hospitalization will be compared. The outcome measures from Azuar et al[21] and Busch et al[5] will provide information for the control group and intervention group respectively. The primary outcome will be analyzed using a 1-way Analysis of Variance (ANOVA) pairwise to compare equality for more than 2 proportions[29]. Results will be analyzed using intention-to-treat analysis to preserve the benefit of randomization[11,12]. Baseline characteristics and secondary outcomes will also be analyzed using ANOVA to compare proportions and means between each group as appropriate.

2.4 Conclusion

Overall, there are positive clinical outcomes in the treatment of AUD in both oral naltrexone and extended-release naltrexone. Both of these medications have been effective in reducing alcohol consumption and cravings but few studies directly compare the two formulations. For the studies that do compare these formulations, there are mixed results regarding the difference in outcomes between the two. There are also no control groups used in these studies which challenges our ability to determine the effectiveness of either formulation in managing AUD. In addition, of the available studies, many are descriptive, observational, or retrospective designs, all of which can introduce bias in the data. These studies tend to focus on the outpatient setting

or a veteran population which may not be useful for a general adult inpatient population. Finally, some feasibility studies look at settings outside of primary care that provide opportunities for intervention but only focus on the implementation process or are not set up with high enough power to determine the effectiveness of the intervention. This results in an inability to provide clear guidance for initiating naltrexone in the inpatient setting. Overall, there is further research is needed in the general adult population with AUD in the inpatient setting to help guide providers on how to intervene in this patient population.

2.5 References

1. Anton RF, O'Malley SS, Ciraulo DA, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA. May 3 2006;295(17):2003-17. doi:10.1001/jama.295.17.2003

2. O'Malley SS, Corbin WR, Leeman RF, et al. Reduction of alcohol drinking in young adults by naltrexone: a double-blind, placebo-controlled, randomized clinical trial of efficacy and safety. J Clin Psychiatry. Feb 2015;76(2):e207-13. doi:10.4088/JCP.13m08934

3. Malone M, McDonald R, Vittitow A, et al. Extended-release vs. oral naltrexone for alcohol dependence treatment in primary care (XON). Contemp Clin Trials. Jun 2019;81:102-109. doi:10.1016/j.cct.2019.04.006

4. Beatty A, Stock C. Efficacy of long-acting, injectable versus oral naltrexone for preventing admissions for alcohol use disorder. Article. Ment Health Clin. 2017;7(3):106-110. doi:10.9740/mhc.2017.05.106

5. Busch AC, Denduluri M, Glass J, et al. Predischarge Injectable Versus Oral Naltrexone to Improve Postdischarge Treatment Engagement Among Hospitalized Veterans with Alcohol Use Disorder: A Randomized Pilot Proof-of-Concept Study. Comparative Study, Randomized Controlled Trial. Alcoholism: Clinical & Experimental Research. Jul 2017;41(7):1352-1360.

6. Beauchamp GA, Laubach LT, Esposito SB, et al. Implementation of a Medication for Addiction Treatment (MAT) and Linkage Program by Leveraging Community Partnerships and Medical Toxicology Expertise. Article. J Med Toxicol. 2021;17(2):176-184. doi:10.1007/s13181-020-00813-4

7. Anderson ES, Chamberlin M, Zuluaga M, et al. Implementation of Oral and Extended-Release Naltrexone for the Treatment of Emergency Department Patients With Moderate to Severe Alcohol Use Disorder: Feasibility and Initial Outcomes. Ann Emerg Med. Dec 2021;78(6):752-758. doi:10.1016/j.annemergmed.2021.05.013

8. Stephens JR, Moore C, Stepanek KV, et al. Implementation of a Process for Initiating Naltrexone in Patients Hospitalized for Alcohol Detoxification or Withdrawal. J Hosp Med. Apr 2018;13(4):221-228. doi:10.12788/jhm.2900

9. Terasaki D, Loh R, Cornell A, Taub J, Thurstone C. Single-dose intravenous ketamine or intramuscular naltrexone for high-utilization inpatients with alcohol use disorder: pilot trial feasibility and readmission rates. Article. Addict Sci Clin Pract. 2022;17(1)64. doi:10.1186/s13722-022-00345-y

10. Wei J, Defries T, Lozada M, Young N, Huen W, Tulsky J. An inpatient treatment and discharge planning protocol for alcohol dependence: efficacy in reducing 30-day readmissions and emergency department visits. J Gen Intern Med. Mar 2015;30(3):365-70. doi:10.1007/s11606-014-2968-9

11. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c869. doi:10.1136/bmj.c869

12. McCoy CE. Understanding the Intention-to-treat Principle in Randomized Controlled Trials. West J Emerg Med. Oct 2017;18(6):1075-1078. doi:10.5811/westjem.2017.8.35985

13. Chen J, McDonald RD, Obi R, et al. Extended-release vs. oral naltrexone for alcohol dependence treatment in primary care. Conference Abstract. Drug and Alcohol Dependence. 01 Feb 2017;171:e39.

14. Association AP. Diagnostic and Statistical Manual of Mental Disorders. Fifth ed. Diagnostic and Statistical Manual of Mental Disorders.

15. VIVITROL (naltrexone for extended-release injectable suspension), for intramuscular use [package insert]. Waltham, MA: Alkermes, Inc.; 2022.

16. REVIA (naltrexone hydrochloride tablets USP) [package insert]. Pomona, New York: DURAMED PHARMACEUTICALS, INC. subsidiary of Barr Pharmaceuticals, Inc.; 2013.

17. Lee JD, Grossman E, DiRocco D, et al. Extended-release naltrexone for treatment of alcohol dependence in primary care. J Subst Abuse Treat. Jul 2010;39(1):14-21. doi:10.1016/j.jsat.2010.03.005

18. Kirchoff RW, Mohammed NM, McHugh J, et al. Naltrexone Initiation in the Inpatient Setting for Alcohol Use Disorder: A Systematic Review of Clinical Outcomes. Mayo Clin Proc Innov Qual Outcomes. Apr 2021;5(2):495-501. doi:10.1016/j.mayocpiqo.2021.01.013

19. Leighty AE, Ansara ED. Treatment outcomes of long-acting injectable naltrexone versus oral naltrexone in alcohol use disorder in veterans. Ment Health Clin. Nov 2019;9(6):392-396. doi:10.9740/mhc.2019.11.392

20. Roozen HG, de Waart R, van den Brink W. Efficacy and tolerability of naltrexone in the treatment of alcohol dependence: oral versus injectable delivery. Eur Addict Res. 2007;13(4):201-6. doi:10.1159/000104882

21. Azuar J, Questel F, Hispard E, Scott J, Vorspan F, Bellivier F. Hospital Stay and Engagement in Outpatient Follow-Up After Alcohol Emergency Detox: A 1-Year Comparison Study. Alcohol Clin Exp Res. Feb 2016;40(2):418-21. doi:10.1111/acer.12962

22. Stewart H, Mitchell BG, Ayanga D, Walder A. Veteran adherence to oral versus injectable AUD medication treatment. Ment Health Clin. May 2021;11(3):194-199. doi:10.9740/mhc.2021.05.194

23. Bryson WC, McConnell J, Korthuis PT, McCarty D. Extended-release naltrexone for alcohol dependence: persistence and healthcare costs and utilization. Am J Manag Care. Jun 2011;17 Suppl 8(Suppl 8):S222-34.

24. Chang G, Crawford M, Pitts M, Schein AZ, Goodwin K, Enggasser JL. Adherence to extended release naltrexone: Patient and treatment characteristics. Article. Am J Addict. 2018;27(6):524-530. doi:10.1111/ajad.12786

25. Walker JR, Korte JE, McRae-Clark AL, Hartwell KJ. Adherence across FDA-approved medications for alcohol use disorder in a veterans administration population. Article. J Stud Alcohol Drugs. 2019;80(5):572-577. doi:10.15288/jsad.2019.80.572

26. Miller PM, Book SW, Stewart SH. Medical treatment of alcohol dependence: a systematic review. Int J Psychiatry Med. 2011;42(3):227-66. doi:10.2190/PM.42.3.b

27. Murphy CEt, Wang RC, Montoy JC, Whittaker E, Raven M. Effect of extended-release naltrexone on alcohol consumption: a systematic review and meta-analysis. Addiction. Feb 2022;117(2):271-281. doi:10.1111/add.15572

28. Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA. May 14 2014;311(18):1889-900. doi:10.1001/jama.2014.3628

29. Chow S SJ, Wang H. Sample Size Calculations in Clinical Research. 2nd ed. Chapman & Hall/CRC Biostatistics Series. 2008.

Chapter 3: Methods

3.1 Study Design

This study will be an open-label, randomized clinical trial to investigate the difference in outpatient treatment follow-up rates for alcohol use disorder (AUD) in hospitalized adults who are referred to outpatient treatment alone or in combination with oral or extended-release naltrexone. We will screen patients diagnosed with AUD on any inpatient medicine and hospitalist service at Yale New Haven Hospital York Street Campus and St. Raphael Campus. Eligible patients will be randomized to one of three study arms: oral naltrexone plus referral to outpatient treatment, extended-release naltrexone plus referral to outpatient treatment, and referral to outpatient treatment alone. Patients will be followed for 12 weeks following discharge with scheduled visits at study entry, 4 weeks post-discharge, 6 weeks post-discharge, and 12 weeks post-discharge.

3.2 Study Population and Sampling

The study population will consist of hospitalized patients aged 18 to 55 years who are admitted to any medicine service at Yale New Haven Hospital's York Street Campus and St. Raphael Campus with a clinical diagnosis of AUD according to criteria from the current Diagnostic and Statistical Manual of Mental Disorders (DSM-V). Full selection criteria is listed below and participants must meet all criteria for study entry. Sampling will be nonrandom convenience sampling for feasibility purposes.

3.2.1 Inclusion Criteria

a. Patients aged 18 to 55 years
b. Patients who meet criteria for AUD according to the DSM-V[1]

c. Patients currently hospitalized that plan to discharge into the community

3.2.2 Exclusion Criteria

a. Patients who are currently pregnant, breastfeeding, or plan to conceive within the next 6 months
b. Patients who are already receiving naltrexone
c. Patients who are prescribed another medication for the treatment of AUD including but not limited to naltrexone, acamprosate, disulfiram, gabapentin, topiramate, baclofen, and ondansetron
    a. Patients who are prescribed any of the above medications for an indication other than the treatment of AUD are still eligible for study
d. Patients who are already participating in outpatient treatment for AUD
e. Patients who are actively using opioids, have used opioids within the past 10 days, or have a positive urine toxicology for opioids, fentanyl, and/or oxycodone within the last 10 days
f. Patients with a history of allergic reaction to naltrexone
g. Patients who are planning to discharge to an inpatient rehabilitation center
h. Patients with impaired liver function defined by:
    a. Liver function tests (total bilirubin, direct bilirubin, ALT, AST, and alkaline phosphatase) $\geq$ 3 times the upper limit of normal AND/OR
    b. Patients with acute hepatitis, severe liver dysfunction, or liver failure
i. Patients unable to take oral medication

3.3 Recruitment

Recruitment will primarily rely on referrals from providers on the hospitalist service and addiction medicine inpatient consult service. An effort will be made to include a representative sample of the general medicine inpatient population. We will use email, educational training sessions, and word-of-mouth to make the general medicine hospitalist service and addiction medicine inpatient consult team aware of the study. Study personnel contact information will be provided to refer potential patients. Providers can refer patients by contacting study personnel through Health Insurance Portability and Accountability Act of 1996 (HIPAA)-approved communication venues including email, the Mobile Heart Beat application, and telephone. Notification of a referral will be followed by a pre-screening process to confirm eligibility criteria based on chart review. Once a patient is determined to be eligible, study personnel who are delegated to give consent will meet with the patient to go over the study details and consent form.

3.4 Informed Consent

Informed consent will be obtained for each patient using the form in Appendix B. An investigator or delegated study team member will meet with potential participants to discuss the study, answer questions, and complete informed consent should the patient decide to enroll. The process of informed consent is ongoing. Patients will be able to opt out of participation at any point without any change in care from their treatment team. Opting out of participation will stop data collection for that participant starting on the day they request to opt out of the study. Participants are not required to give a reason for opting out of the study early and their care will not be affected by opting out of research.

3.5 Subject Protection and Confidentiality

Protecting the privacy and health information of study subjects will be a top priority of this study. This study will be submitted to the Yale New Haven Health Institutional Review Board (IRB) for review and potential approval. All investigators and study team members will be required to complete Human Research training through Yale University including Human Subjects Protection, HIPAA, and Good Clinical Practice before working on the study. The study will have a delegation log to keep track of all study personnel, their training, and primary investigator approval for task delegation on this study. All study material and data, if electronic, will be stored in password protected computers. If the data is printed, it will be stored in locked offices and cabinets. Study data and material will only be accessible to study personnel who are delegated to view this information and required to use it within their role.

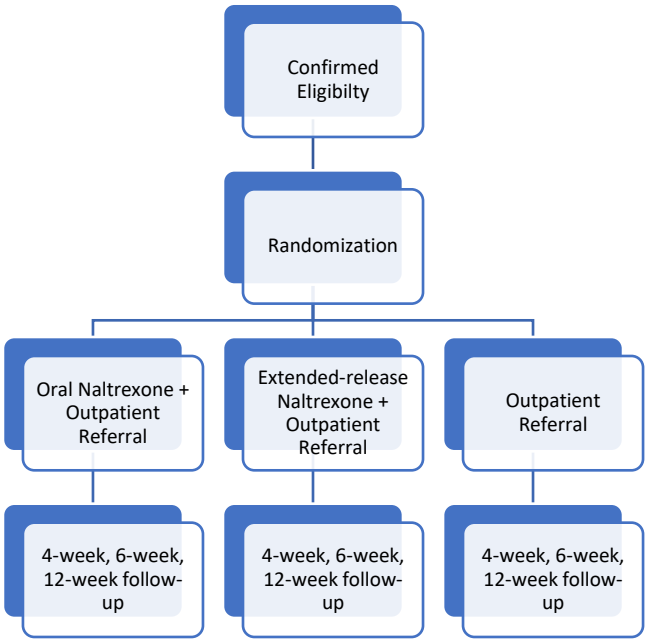
A 6-digit number will be assigned to each study participant to maintain privacy in study documents and electronic databases. A separate log to identify patients and their study ID numbers will be kept by the principal investigator in a locked cabinet. Otherwise, patient identifying information and study ID numbers will not be found on the same document or within the electronic databases used in the study.

3.6 Randomization

Participants will be randomized 1:1:1 to oral naltrexone plus referral to outpatient treatment, extended-release naltrexone plus referral to outpatient treatment, and referral to outpatient treatment alone. Participants will be randomized to a study arm by a computer-generated sequence to prevent the investigators or the study team from influencing allocation. The study team will only be able to reveal the treatment arm allocation when a participant is deemed

eligible for study by at least one study team member and a study investigator delegated to approve eligibility.

Graph 1. *Enrollment Process Flow Chart*



3.7 Blinding

Blinding will not be used in this study due to ethical and feasibility concerns. The treating physician, pharmacist, and treatment team will not be blinded to the study arm to help the participant with any questions or concerns regarding the medication. Study personnel will not be blinded to study arms to allow for confirmation of medication adherence using the electronic medical record and contacting pharmacies and clinics. Participants will not be blinded to their assigned study arm as it would be unethical to require all study participants to receive placebo extended-release injections solely for the purpose of blinding subjects.

3.8 Intervention

The interventions for this study include referral to outpatient AUD treatment, oral naltrexone, and extended-release naltrexone. All participants will choose their outpatient treatment clinic of

choice in collaboration with social work, inpatient addiction medicine consult team, and/or Health Promotion Advocates. The preferred outpatient treatment clinic and the contact information for the clinic will be recorded to obtain documentation of attendance. Oral and extended-release naltrexone will be prescribed by the treating provider and will be paid per standard of care. The participant's pharmacy and contact information will be recorded to obtain medication dispense history if not already listed in the patient's electronic medical record. Participants randomized to the oral naltrexone arm will take one 50mg tablet daily. Participants in the extended-naltrexone arm will be dosed 380mg in an intramuscular injection every 4 weeks. Participants will be monitored for adverse events starting at the administration of the first dose for participants in the oral or extended-release naltrexone arms, or at study entry for the referral to treatment alone arm.

3.9 Schedule of Assessments

3.9.1 Screening Visit

The screening visit will be conducted while the patient is admitted to the hospital. Study personnel will meet with patients in-person or via telephone to discuss the study and obtain consent. No other study assessments can be performed until consent is obtained. Study personnel will also obtain baseline characteristics and confirm eligibility during this visit. The screening visit and study entry visit can be completed on the same day.

3.9.2 Study Entry Visit

The study entry visit will take place prior to the participant being discharged. The visit will include confirmation of eligibility criteria, completion of the study survey, and randomization to one of the three treatment arms. Ideally, the study entry visit should be

completed as close to discharge as possible to ensure that the discharge plan remains the same and the participant continues to be eligible. Participants in the oral naltrexone and extended-release naltrexone arms should receive their first dose of medication on the day of discharge if feasible for the treatment and study teams.

3.9.3 Follow-Up Visits

There will be total of three follow-up visits required for this study. Follow-up visits will be completed at week 4, week 6, and week 12 following discharge. Follow-up visits will include a ± 7 day window to allow for flexibility. Study surveys will be completed in-person or via telephone with each participant depending on patient preference and availability of study personnel. The electronic medical record, pharmacy records, and outpatient clinic records will be obtained to confirm outpatient follow-up attendance and medication adherence. Every effort should be made to contact the patient via telephone to prevent loss to follow up.

Table 1. *Schedule of Assessments*

Schedule of Assessments					
	Screening Day -14 to 0	**Study Entry Day 0**	**4-week follow-up Day 28 ± 7 days**	**6-week follow-up Day 42 ± 7 days**	**12-week follow-up Day 84 ± 7 days**
Study Consent	**X**				
Confirmation of Eligibility Criteria	**X**	**X**			
Baseline Characteristics	**X**				
Randomization		**X**			
Study Survey		**X**	**X**	**X**	**X**
Confirmation of Outpatient Treatment			**X**	**X**	**X**
Medication Dispense History[a]			**X**	**X**	**X**

[a]Oral naltrexone and extended-release naltrexone arms only

3.10 Study Variables and Measures

3.10.1 Primary Outcome

The primary dependent variable in this study will be the participants attending at least one outpatient treatment appointment, either in person or via telehealth, for AUD treatment following their hospitalization within 12 weeks of discharge. We will confirm attendance of outpatient treatment by documentation of the visit from the outpatient treatment clinic. The primary independent variable in this study will be the initiation of oral naltrexone, extended-release naltrexone, or no pharmacologic treatment prior to discharge. The primary outcome of interest is the proportion of participants in each treatment arm who attend at least one outpatient follow-up appointment for treatment of AUD.

3.10.2 Secondary Outcomes

Secondary outcome variables in this study will include adherence to medication for AUD treatment and number of heavy drinking days per week at 4 weeks, 6 weeks, and 12 weeks post-discharge. Medication adherence will be studied in the oral naltrexone and extended-naltrexone treatment arms. Medication adherence will be assessed by medication dispense history for oral naltrexone and documentation of extended-release naltrexone injection. The mean percentage of patients that adherent to medication within the oral naltrexone and extended-release naltrexone groups. The number of heavy drinking days per week will be self-reported. The mean number of heavy drinking days per week in each group (oral naltrexone, extended-release naltrexone, and referral to treatment alone) will be compared. The mean number of heavy drinking days per week in each group (oral naltrexone plus referral to outpatient treatment, extended-release naltrexone plus referral to outpatient treatment, and referral to outpatient treatment alone) will be compared.

3.10.3 Potential Confounding Variables

Potential confounding variables include sociodemographic characteristics such as age, gender, race, ethnicity, employment status, insurance status, household income, and housing status. Other potential confounding variables include medical comorbidities, concomitant psychiatric comorbidities, concomitant substance use disorder, severity of AUD, duration of AUD based on similar previous studies as discussed in Chapter 2. These potential confounding variables will be included in baseline characteristics to ensure that study groups are similar. It is also possible that there are other potential confounding variables that have not been identified yet.

3.11 Data Collection

Data will be obtained through participant questionnaires, phone interviews, and electronic medical records. Each participant will be assigned a 6-digit study ID that will be used for study documents and data collection. We will use Research Electronic Data Capture (REDCap) to record study information including baseline characteristics, treatment group assignment, study survey responses, and confirmation of outpatient appointment and medication adherence. The following baseline characteristics will be obtained: age at study entry, sex, race, ethnicity, comorbid medical conditions, insurance status (insured or uninsured), employment status (employed or unemployed), housing status (stable or unstable), socioeconomic status (range of household income from $0 – $24, 999, $25,000 – $49,999, $50,000 – 74,999, $75,000 – 99,999, $100,000+). The study survey used at multiple time points throughout the study can be found in Appendix C.

3.12 Sample Size

As discussed in Chapter 2, sample size calculations are completed for 1-way analysis of variance (ANOVA) pairwise statistical analysis to compare multiple proportions. Group A proportion is based on a control group with a proportion of 0.57^3 and Group B proportion is based on an intervention group with a proportion of 0.826^4. The number of pairwise comparisons, τ, for this calculation is 3 based on the 3 study arms. A sample size of 62 is calculated using the Power and Sample Size online calculator as referenced in Appendix D. To account for dropout and anticipated loss to follow-up, an additional 20% of 62, 12.4, is added to 62 and rounded up to the nearest whole number giving a final sample size of 75.

3.13 Statistical Analysis

Baseline characteristics will be analyzed using ANOVA to compare multiple proportions and means as appropriate. Data from this study will be analyzed using an intention-to-treat analysis. The primary outcome will be analyzed using 1-way ANOVA pairwise statistical analysis for more than two proportions to compare the three treatment arms. For secondary outcomes, two different statistical tests will be used. Medication adherence between the oral naltrexone and extended-release naltrexone groups will be analyzed using a paired two-sample t test. Mean number of drinks per week within all three groups will be analyzed using 1-way ANOVA pairwise with 2-sided equality.

3.14 Timeline and Resources

The timeline for this study will include a 12-month recruitment period, 3-month follow up data collection period for each patient, and 6-month statistical analysis period. The target enrollment date for the first participant will be August 2023 with the last participant enrolled in August 2024. The last follow-up visit completed is estimated for December 2024 and statistical

analysis should be completed in June 2025. Resources for this study will include study personnel, IRB, technology to access the electronic medical record, and a biostatistician for statistical analysis. We will use the Yale IRB for approval and oversight of the protocol including amendments. Study personnel will require protocol training, delegation to conduct study tasks, and access to the electronic medical record system and REDCap. They will need to be on-site or available by phone for study consent, obtain baseline characteristics, and collect the baseline survey for each patient. Study personnel will also need to be available to conduct phone interviews at 4-week, 6-week, and 12-week follow-up visits and have access to electronic medical records to obtain medication dispense history and outpatient clinic visit information.

3.15 References

1. Association AP. Diagnostic and Statistical Manual of Mental Disorders. Fifth ed. Diagnostic and Statistical Manual of Mental Disorders.

2. Chow S SJ, Wang H. Sample Size Calculations in Clinical Research. 2nd ed. Chapman & Hall/CRC Biostatistics Series. 2008.

3. Azuar J, Questel F, Hispard E, Scott J, Vorspan F, Bellivier F. Hospital Stay and Engagement in Outpatient Follow-Up After Alcohol Emergency Detox: A 1-Year Comparison Study. Alcohol Clin Exp Res. Feb 2016;40(2):418-21. doi:10.1111/acer.12962

4. Busch AC, Denduluri M, Glass J, et al. Predischarge Injectable Versus Oral Naltrexone to Improve Postdischarge Treatment Engagement Among Hospitalized Veterans with Alcohol Use Disorder: A Randomized Pilot Proof-of-Concept Study. Comparative Study, Randomized Controlled Trial. Alcoholism: Clinical & Experimental Research. Jul 2017;41(7):1352-1360.

Chapter 4: Discussion

4.1 Limitations

It is important to note the limitations of this study to understand how to interpret study results for use in clinical practice for treating alcohol use disorder (AUD). One limitation of this study is that is confined to one hospital system in one city in the United States that may differ in population and accessibility compared to other cities and regions. Different state laws, views, and efforts to intervene in AUD may affect the way other regions are able to adapt a similar intervention. In addition, the use of a dedicated addiction medicine service at Yale New Haven Hospital is also unique to the health system that may not be available everywhere. It is important to recognize how these resources could increase access to MAUD and affect the ability to complete the study more easily than other health systems and clinical sites around the country.

There are also a few limitations to the study methods. One limitation is that the study includes a control group meaning a third of enrolled participants will not be receiving MAUD. In addition, this study only includes naltrexone which allows us to compare the effectiveness of both naltrexone formulations but does not include all MAUD options. Based on the results of this study, the hope is to compare the effectiveness of all MAUD in future studies. The open-label study design is also a limitation that may introduce differential bias. There are both ethical and feasibility concerns with blinding in this study. The primary concern is that participants cannot be blinded to the assigned study arm since one arm includes an intramuscular injection every 4 weeks. The risk of receiving an unnecessary injection outweighs the benefit of the study. Another limitation is that the secondary outcome of heavy drinking days per week will be self-reported, which may not be entirely accurate due to recall bias. Finally, the anticipated sample

size is small, which means further multi-center randomized trials will be needed to test the effects of oral versus extended-release naltrexone in a larger, more regionally diverse sample size.

4.2 Generalizability

The goal of this study is to provide evidence that can be applied to the management of AUD at different inpatient sites within the United States. The plan is to recruit a representative sample and control for potential confounding variables. It is important to note that the sample size may not be large enough to reduce error, therefore reducing generalizability of study results. Additionally, although an addiction medicine consult team will be available at this study site, the main intervention and outcomes of this study do not require a dedicated consult service. The results of this study should be applicable to a variety of inpatient settings as any general medicine provider can prescribe naltrexone or other MAUD.

4.3 Conclusion

More randomized clinical trials are needed to examine the initiation of MAUD in the inpatient setting and its effect on linking patients to outpatient treatment. While we know these medications can be effective at reducing alcohol consumption in patients with AUD, it is only helpful if people use the medication and continue treatment. MAUD should be compared for adherence rates to understand how these medications are used in real life settings. This can help us understand potential confounding variables and barriers to patients starting and continuing medication. Future studies should be done on a larger scale and include a variety of study sites across different health systems across in the United States.

There is also a need to educate clinicians on MAUD in a variety of healthcare settings. Studies have shown the efficacy of naltrexone in improving clinical outcomes, but clinicians continue to prescribe MAUD at low rates. Increasing the MAUD prescribing rate will require education as well as a cultural shift to help providers outside of addiction medicine feel comfortable screening for AUD and using FDA-approved medication to treat. Providing in-person or virtual trainings to providers working in the inpatient setting can help address this issue. It is also important to confirm that oral naltrexone and extended-release naltrexone are available on hospital formulary, so providers have access to prescribe these medications.

In summary, AUD is a chronic condition that requires a variety of therapies, including pharmacotherapy, for management including pharmacotherapy. While there are multiple FDA-approved medications with proven efficacy to reduce alcohol consumption, clinical providers have been slow to prescribe them. The inpatient setting provides an opportunity for clinicians to intervene in AUD and initiate patients on MAUD, including oral and extended-release naltrexone. Previous studies show that these medications can be effective in reducing alcohol consumption, so it is important to study how initiating these medications affect other outcomes including linkage to outpatient treatment. This study will be one of the first of its kind to directly compare the initiation of oral and extended-release in a general medical inpatient setting.

Appendix A: DSM-V Criteria for Alcohol Use Disorder

DSM-V AUD Criteria

A problematic pattern of alcohol use leading to clinically significant impairment or distress as manifested by at least 2 of the following, occurring within a 12-month period:

1. Alcohol is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
4. Craving, or a strong desire or urge to use alcohol.
5. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.
7. Important social, occupational, or recreational activities are given up or reduced be-cause of alcohol use.
8. Recurrent alcohol use in situations in which it is physically hazardous.
9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
10. Tolerance, as defined by either of the following:
    i. A need for markedly increased amounts of alcohol to achieve intoxication or de-sired effect.
    ii. A markedly diminished effect with continued use of the same amount of alcohol.
11. Withdrawal, as manifested by either of the following:
    i. The characteristic withdrawal syndrome for alcohol[1]
        A. Cessation of (or reduction in) alcohol use that has been heavy and prolonged.
        B. Two (or more) of the following, developing within several hours to a few days after the cessation of (or reduction in) alcohol use described in Criterion A:
            a. Autonomic hyperactivity (e.g., sweating or pulse rate greater than 100 bpm).
            b. Increased hand tremor.
            c. Insomnia.
            d. Nausea or vomiting.
            e. Transient visual, tactile, or auditory hallucinations or illusions.
            f. Psychomotor agitation.
            g. Anxiety.
            h. Generalized tonic-clonic seizures.
        C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
        D. The signs or symptoms are not attributable to another medical condition and are not better explained by another

mental disorder, including intoxication or withdrawal from another substance

ii. Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms

Severity of alcohol use disorder:

Mild: Presence of 2-3 criteria

Moderate: Presence of 4-5 criteria

Severe: Presence of 6 or more criteria

Appendix B: Consent Form

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH STUDY

YALE UNIVERSITY

YALE UNIVERSITY SCHOOL OF MEDICINE

YALE-NEW HAVEN HOSPITAL

YALE-NEW HAVEN HOSPITAL: SAINT RAPHAEL CAMPUS

Study Title: LINKAGE TO OUTPATIENT TREATMENT FOR INPATIENTS WITH ALCOHOL USE DISORDER STARTED ON NALTREXONE

Principal Investigator (the person who is responsible for this research): Srinivas Muvvala, MD, MPH

Co-investigator: Stephanie Stamatis, PA-S

Research Study Summary:

- We are asking you to join a research study.
- The purpose of this research study is to test the effectiveness of starting patients in the hospital on naltrexone for the treatment of alcohol use disorder.
- Study procedures will include: A review of medical history, prescription history, health visit history, current medications, and questionnaires.
- 5 visits are required.
- These visits will take 5 hours total.
- There are some risks from participating in this study. As with starting any new medication, there may be some side effects or adverse reactions. There is also a risk of breach of privacy. While we are dedicated to keeping your personal health information private, there is the risk that information may reach outside parties.
- The study may have benefits to you including the treatment of alcohol use disorder.
- There are other choices available to you outside of this research. You may be eligible to take oral naltrexone or extended-release naltrexone without participating in this study.
- Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You can also change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.
- If you are interested in learning more about the study, please continue reading, or have someone read to you, the rest of this document. Take as much time as you need before you make your decision. Ask the study staff questions about anything you do not understand. Once you understand the study, we will ask you if you wish to participate; if so, you will have to sign this form.

Why is this study being offered to me?

We are asking you to take part in a research study because **you are an adult with alcohol use disorder and may be eligible to for a medication to treat alcohol use disorder**. We are looking for **75** participants to be part of this research study.

Who is paying for the study?

Yale New Haven Hospital

What is the study about?

The purpose of this study is to learn how effective oral naltrexone and extended-release, or injectable, naltrexone is when started in patients who are in the hospital.

What are you asking me to do and how long will it take?

If you agree to take part in this study, this is what will happen:

- A study team member will review your medical history and medications with you to determine if you are eligible to participate.
- We will ask you about demographic and basic information about yourself.
- We will ask you to complete a survey related to your alcohol use before you start the study and at 4 weeks, 6 weeks, and 12 weeks after starting the study.
- You will be set up for an outpatient treatment visit and asked to attend this visit.
- If you are randomized to a treatment group to receive medication, you will be prescribed the medication. If you are randomized to a treatment group, you will be receiving active medication, not a placebo.

What are the risks and discomforts of participating?

The main risks and discomforts of participating in this study include the adverse effects of the oral naltrexone and extended-release naltrexone. These include:

- Vulnerability to opioid overdose
- Injection site reactions
- Precipitation of opioid withdrawal
- Hepatotoxicity
- Depression and suicidality
- Reversal of extended-release naltrexone blockade for pain management
- Eosinophilic pneumonia
- Hypersensitivity reactions including anaphylaxis

How will I know about new risks or important information about the study?

We will tell you if we learn any new information that could change your mind about taking part in this study. We will contact you via telephone should there be new risks or information regarding the study and your participation in it. Clinically relevant research results will also be disseminated via telephone calls as they are made available.

How can the study possibly benefit me?

You may see an improvement in your alcohol use disorder from participating in this study.

How can the study possibly benefit other people?

The benefits to science and other people may include a better understanding of how to treat alcohol use disorder in patients who are in the hospital before they are discharged home.

Are there any costs to participation?

If you take part in this study, you will not have to pay for any services, supplies, study procedures, or care that are provided for this research only (they are NOT part of your routine medical care). However, there may be additional costs to you. These can include costs of transportation and your time to come to the study visits. You or your health insurance must pay for services, supplies, procedures, and care that are part of your routine medical care. You will be responsible for any co-payments required by your insurance.

You will not have to pay for taking part in this study. The only costs include transportation and your time coming to the study visits.

Your study doctor, a member of the study team, or a member of the research billing team will be glad to answer your questions about whether services or tests performed during the course of a research study will be billed to your insurance provider or to you, or about any bills that you may receive during your participation in a research study. Please call the research billing team at 1-877-TRIALS0 (1-877-874-2560) with any questions. You may also contact your insurance provider directly.

Will I be paid for participation?

You will not be paid for taking part in this study.

What are my choices if I decide not to take part in this study?

Instead of participating in this study, you have some other choices.

You could:

- Get treatment without being in a study. Naltrexone, both oral and extended-release forms, are FDA-approved for the treatment of alcohol use disorder. There are other medications and non-medication treatments available for alcohol use disorder that you may be eligible for.
- Take part in another study.
- Receive comfort care only, without any treatment for your disease.

How will you keep my data safe and private?

We will keep information we collect about you confidential. We will share it with others if you agree to it or when we have to do it because U.S. or State law requires it. For example, we will tell somebody if you we learn that you are hurting a child or an older person.

We will use unique identifiers for databases to protect your information. Your personal health information will only be made available to necessary research personnel. All research databases and medical charts will be password protected if electronic or kept in a locked cabinet in the research office if printed.

When we publish the results of the research or talk about it in conferences, we will not use your name. If we want to use your name, we would ask you for your permission.

What Information Will You Collect About Me in this Study?

The information we are asking to use and share is called "Protected Health Information." It is protected by a federal law called the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). In general, we cannot use or share your health information for research without your permission. If you want, we can give you more information about the Privacy Rule. Also, if you have any questions about the Privacy Rule and your rights, you can speak to Yale Privacy Officer at 203-432-5919.

The specific information about you and your health that we will collect, use, and share includes:

- Research study records
- Medical and laboratory records of only those services provided in connection with this study
- The entire research record and any medical records held by Yale New Haven Hospital and records from other institutions available via Epic
- Records about phone calls made as part of this research
- Records about your study visits
- Information obtained during this research regarding:
    - HIV / AIDS test results
    - Hepatitis infection
    - Sexually transmitted diseases
    - Other reportable infectious diseases
    - Physical exams
    - Laboratory, x-ray, and other test results
    - Diaries and questionnaires
    - The diagnosis and treatment of a mental health condition

- Use of illegal drugs or the study of illegal behavior
- Records about any study drug you received and other medications prescribed

How will you use and share my information?

We will use your information to conduct the study described in this consent form.
We may share your information with:

- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University, the Yale Human Research Protection Program and the Institutional Review Board (the committee that reviews, approves, and monitors research on human participants), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- The U.S. Food and Drug Administration (FDA) This is done so that the FDA can review information about Naltrexone involved in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- The study sponsor or manufacturer of study drug/device
- Drug regulatory agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Health care providers who provide services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Principal Investigator of the study
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study

We will do our best to make sure your information stays private. But, if we share information with people who do not have to follow the Privacy Rule, your information will no longer be protected by the Privacy Rule. Let us know if you have questions about this. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

Why must I sign this document?

By signing this form, you will allow researchers to use and disclose your information described above for this research study. This is to ensure that the information related to this research is available to all parties who may need it for research purposes. You always have the right to review and copy your health information in your medical record.

What if I change my mind?

The authorization to use and disclose your health information collected during your participation in this study will never expire. However, you may withdraw or take away your permission at any time. You may withdraw your permission by telling the study staff or by writing to Stephanie Stamatis at the Yale University, New Haven, CT 06520.

If you withdraw your permission, you will not be able to stay in this study but the care you get from your doctor outside this study will not change. No new health information identifying you will be gathered after the date you withdraw. Information that has already been collected may still be used and given to others until the end of the research study to ensure the integrity of the study and/or study oversight.

Who will pay for treatment if I am injured or become ill due to participation in the study?

Should you become injured or ill due to participation in this study, medical care will be billed to your insurance.

What if I want to refuse or end participation before the study is over?

Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment. Not participating or withdrawing later will not harm your relationship with your own doctors or with this institution.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part.

The researchers may withdraw you from participating in the research if necessary. If there are any medical concerns or you develop serious side effects due to the study medication, we may withdraw you from participation.

What will happen with my data if I stop participating?

If you stop participating in the study we will no longer collect data from you but previous data collected will continue to be used in analysis.

Who should I contact if I have questions?

Please feel free to ask about anything you don't understand.

If you have questions later or if you have a research-related problem, you can call or email the Principal Investigator.

If you have questions about your rights as a research participant, or you have complaints about this research, you call the Yale Institutional Review Boards at (203) 785-4688 or email hrpp@yale.edu

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Authorization and Permission

Your signature below indicates that you have read this consent document and that you agree to be in this study.

We will give you a copy of this form.

Participant Printed Name	Participant Signature	Date

Person Obtaining Consent Printed Name	Person Obtaining Consent Signature	Date

Appendix C: Study Survey

STUDY SURVEY

STUDY ID: _____

Have you attended an outpatient appointment for alcohol use disorder treatment following your recent hospitalization? ☐ Yes ☐ No ☐ N/A (study entry visit)

Please answer the following questions using whole numbers i.e. (0, 1, 2, 3, 4, 5…). A standard drink is 12 fluid ounces of regular beer, 8-9 fluid ounces of malt liquor, 5 fluid ounces of wine, or 1.5 fluid ounces of 80-proof spirits.

1. How many drinks did you have in the past week? ____
2. How many drinks did you have per day, on average, in the past week? ____
3. Please answer one of the following:
    a. Women: How many days in the past week did you have 4 or more drinks per day? ____
    b. Men: How many days in the past week did you have 5 or more drinks per day? _____

Appendix D: Sample Size Calculation

1-Way ANOVA Pairwise

$$n = (p_A(1 - p_A) + p_B(1 - p_B))(\frac{z_{1-\frac{\alpha}{2\tau}} - z_{1-\beta}}{p_A - p_B})^2$$

Group A Proportion (p_A) = 0.826

Group B Proportion (p_B) = 0.57

Number of Pairwise Comparisons (τ) = 3

Type I Error (α) = 0.05

Power (1 – β) = 80%

Bibliography

Anderson ES, Chamberlin M, Zuluaga M, et al. Implementation of Oral and Extended-Release Naltrexone for the Treatment of Emergency Department Patients With Moderate to Severe Alcohol Use Disorder: Feasibility and Initial Outcomes. Ann Emerg Med. Dec 2021;78(6):752-758. doi:10.1016/j.annemergmed.2021.05.013

Anton RF, O'Malley SS, Ciraulo DA, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA. May 3 2006;295(17):2003-17. doi:10.1001/jama.295.17.2003

Association AP. Diagnostic and Statistical Manual of Mental Disorders. Fifth ed. Diagnostic and Statistical Manual of Mental Disorders.

Azuar J, Questel F, Hispard E, Scott J, Vorspan F, Bellivier F. Hospital Stay and Engagement in Outpatient Follow-Up After Alcohol Emergency Detox: A 1-Year Comparison Study. Alcohol Clin Exp Res. Feb 2016;40(2):418-21. doi:10.1111/acer.12962

Barata IA, Shandro JR, Montgomery M, et al. Effectiveness of SBIRT for Alcohol Use Disorders in the Emergency Department: A Systematic Review. West J Emerg Med. Oct 2017;18(6):1143-1152. doi:10.5811/westjem.2017.7.34373

Beatty A, Stock C. Efficacy of long-acting, injectable versus oral naltrexone for preventing admissions for alcohol use disorder. Article. Ment Health Clin. 2017;7(3):106-110. doi:10.9740/mhc.2017.05.106.

Beauchamp GA, Laubach LT, Esposito SB, et al. Implementation of a Medication for Addiction Treatment (MAT) and Linkage Program by Leveraging Community Partnerships and Medical Toxicology Expertise. Article. J Med Toxicol. 2021;17(2):176-184. doi:10.1007/s13181-020-00813-4

Bohm MK, Liu Y, Esser MB, et al. Binge Drinking Among Adults, by Select Characteristics and State — United States, 2018. Vol. 70. 2021. Morbidity and Mortality Weekly Report.

Bryson WC, McConnell J, Korthuis PT, McCarty D. Extended-release naltrexone for alcohol dependence: persistence and healthcare costs and utilization. Am J Manag Care. Jun 2011;17 Suppl 8(Suppl 8):S222-34.

Busch AC, Denduluri M, Glass J, et al. Predischarge Injectable Versus Oral Naltrexone to Improve Postdischarge Treatment Engagement Among Hospitalized Veterans with Alcohol Use Disorder: A Randomized Pilot Proof-of-Concept Study. Comparative Study, Randomized Controlled Trial. Alcoholism: Clinical & Experimental Research. Jul 2017;41(7):1352-1360.

Chang G, Crawford M, Pitts M, Schein AZ, Goodwin K, Enggasser JL. Adherence to extended release naltrexone: Patient and treatment characteristics. Article. Am J Addict. 2018;27(6):524-530. doi:10.1111/ajad.12786

Chen J, McDonald RD, Obi R, et al. Extended-release vs. oral naltrexone for alcohol dependence treatment in primary care. Conference Abstract. Drug and Alcohol Dependence. 01 Feb 2017;171:e39.

Chow S SJ, Wang H. Sample Size Calculations in Clinical Research. 2nd ed. Chapman & Hall/CRC Biostatistics Series. 2008.

Collaborators GBDA. Population-level risks of alcohol consumption by amount, geography, age, sex, and year: a systematic analysis for the Global Burden of Disease Study 2020. Lancet. Jul 16 2022;400(10347):185-235. doi:10.1016/S0140-6736(22)00847-9

Fairbanks J, Umbreit A, Kolla BP, et al. Evidence-Based Pharmacotherapies for Alcohol Use Disorder: Clinical Pearls. Review. Mayo Clin Proc. 2020;95(9):1964-1977. doi:10.1016/j.mayocp.2020.01.030

Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA. May 14 2014;311(18):1889-900. doi:10.1001/jama.2014.3628

Kerr WC, Ye Y, Martinez P, et al. Longitudinal assessment of drinking changes during the pandemic: The 2021 COVID-19 follow-up study to the 2019 to 2020 National Alcohol Survey. Alcohol Clin Exp Res. Jun 2022;46(6):1050-1061. doi:10.1111/acer.14839

Kirchoff RW, Mohammed NM, McHugh J, et al. Naltrexone Initiation in the Inpatient Setting for Alcohol Use Disorder: A Systematic Review of Clinical Outcomes. Mayo Clin Proc Innov Qual Outcomes. Apr 2021;5(2):495-501. doi:10.1016/j.mayocpiqo.2021.01.013

Kranzler HR, Soyka M. Diagnosis and Pharmacotherapy of Alcohol Use Disorder: A Review. JAMA. Aug 28 2018;320(8):815-824. doi:10.1001/jama.2018.11406

Lee JD, Grossman E, DiRocco D, et al. Extended-release naltrexone for treatment of alcohol dependence in primary care. J Subst Abuse Treat. Jul 2010;39(1):14-21. doi:10.1016/j.jsat.2010.03.005

Leighty AE, Ansara ED. Treatment outcomes of long-acting injectable naltrexone versus oral naltrexone in alcohol use disorder in veterans. Ment Health Clin. Nov 2019;9(6):392-396. doi:10.9740/mhc.2019.11.392

Quality CfBHa. Key substance use and mental health indicators in the United States: Results from the 2015 National Survey on Drug Use and Health. Vol. HHS Publication No. SMA 16-4984, NSDUH Series H-51. 2016. http://www.samhsa.gov/data

Malone M, McDonald R, Vittitow A, et al. Extended-release vs. oral naltrexone for alcohol dependence treatment in primary care (XON). Contemp Clin Trials. Jun 2019;81:102-109. doi:10.1016/j.cct.2019.04.006

McCoy CE. Understanding the Intention-to-treat Principle in Randomized Controlled Trials. West J Emerg Med. Oct 2017;18(6):1075-1078. doi:10.5811/westjem.2017.8.35985

Miller PM, Book SW, Stewart SH. Medical treatment of alcohol dependence: a systematic review. Int J Psychiatry Med. 2011;42(3):227-66. doi:10.2190/PM.42.3.b

Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c869. doi:10.1136/bmj.c869

Murphy CEt, Wang RC, Montoy JC, Whittaker E, Raven M. Effect of extended-release naltrexone on alcohol consumption: a systematic review and meta-analysis. Addiction. Feb 2022;117(2):271-281. doi:10.1111/add.15572

National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP). Excessive Alcohol Use. July 11, 2022. https://www.cdc.gov/chronicdisease/resources/publications/factsheets/alcohol.htm#print

Nehring SM, Freeman AM. Alcohol Use Disorder. StatPearls. 2022.

O'Malley SS, Corbin WR, Leeman RF, et al. Reduction of alcohol drinking in young adults by naltrexone: a double-blind, placebo-controlled, randomized clinical trial of efficacy and safety. J Clin Psychiatry. Feb 2015;76(2):e207-13. doi:10.4088/JCP.13m08934

REVIA (naltrexone hydrochloride tablets USP) [package insert]. Pomona, New York: DURAMED PHARMACEUTICALS, INC. subsidiary of Barr Pharmaceuticals, Inc.; 2013.

Roozen HG, de Waart R, van den Brink W. Efficacy and tolerability of naltrexone in the treatment of alcohol dependence: oral versus injectable delivery. Eur Addict Res. 2007;13(4):201-6. doi:10.1159/000104882

Rosner S, Hackl-Herrwerth A, Leucht S, Vecchi S, Srisurapanont M, Soyka M. Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev. Dec 8 2010;(12):CD001867. doi:10.1002/14651858.CD001867.pub3

Slade T, Chapman C, Swift W, Keyes K, Tonks Z, Teesson M. Birth cohort trends in the global epidemiology of alcohol use and alcohol-related harms in men and women: systematic review and metaregression. BMJ Open. Oct 24 2016;6(10):e011827. doi:10.1136/bmjopen-2016-011827

Stephens JR, Moore C, Stepanek KV, et al. Implementation of a Process for Initiating Naltrexone in Patients Hospitalized for Alcohol Detoxification or Withdrawal. J Hosp Med. Apr 2018;13(4):221-228. doi:10.12788/jhm.2900

Stewart H, Mitchell BG, Ayanga D, Walder A. Veteran adherence to oral versus injectable AUD medication treatment. Ment Health Clin. May 2021;11(3):194-199. doi:10.9740/mhc.2021.05.194

Terasaki D, Loh R, Cornell A, Taub J, Thurstone C. Single-dose intravenous ketamine or intramuscular naltrexone for high-utilization inpatients with alcohol use disorder: pilot trial feasibility and readmission rates. Article. Addict Sci Clin Pract. 2022;17(1)64. doi:10.1186/s13722-022-00345-y

Trowbridge P, Weinstein ZM, Kerensky T, et al. Addiction consultation services – Linking hospitalized patients to outpatient addiction treatment. Article. J Subst Abuse Treat. 2017;79:1-5. doi:10.1016/j.jsat.2017.05.007

VIVITROL (naltrexone for extended-release injectable suspension), for intramuscular use [package insert]. Waltham, MA: Alkermes, Inc.; 2022.

Walker JR, Korte JE, McRae-Clark AL, Hartwell KJ. Adherence across FDA-approved medications for alcohol use disorder in a veterans administration population. Article. J Stud Alcohol Drugs. 2019;80(5):572-577. doi:10.15288/jsad.2019.80.572

Wakeman SE, Herman G, Wilens TE, Regan S. The prevalence of unhealthy alcohol and drug use among inpatients in a general hospital. Subst Abuse. 2020/07/02 2020;41(3):331-339. doi:10.1080/08897077.2019.1635961

Wei J, Defries T, Lozada M, Young N, Huen W, Tulsky J. An inpatient treatment and discharge planning protocol for alcohol dependence: efficacy in reducing 30-day readmissions and emergency department visits. J Gen Intern Med. Mar 2015;30(3):365-70. doi:10.1007/s11606-014-2968-9

Witkiewitz K, Heather N, Falk DE, et al. World Health Organization risk drinking level reductions are associated with improved functioning and are sustained among patients with mild, moderate and severe alcohol dependence in clinical trials in the United States and United Kingdom. Addiction. Sep 2020;115(9):1668-1680. doi:10.1111/add.15011