VA Cooperative Studies Program #576

VA Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D)

STUDY PROTOCOL

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EXECUTIVE SUMMARY

Background: The consequences of inadequately treated major depressive disorder (MDD) to America’s Veterans and to the system of healthcare built to serve their needs are profound and disturbing. MDD is among the most disabling and widespread of mental disorders, causing as much or more functional impairment as chronic heart disease and affecting over 300,000 VA patients per year. There are many first-step options available to treat depression. Yet, only about one in three patients with MDD respond adequately to their initial treatment; thus, the majority requires additional treatment regimens, the subject of this study.

Inadequate treatment of MDD amplifies suffering, disability, and all-cause and suicide mortality. In addition, poor outcomes due to inadequate treatment are a burden to the healthcare system through increased pressure on emergency, inpatient, and outpatient psychiatric and general medical services. Poverty, coexisting illness, and trauma have all been demonstrated to complicate treatment and to reduce the likelihood of remission. The Nation’s Veteran population shows high rates of these conditions. For patients who do not have an acceptable outcome to their initial antidepressant, several second-step treatment strategies are available; but the evidence in support of any particular approach is remarkably thin. VAST-D proposes to examine the safety and efficacy of the three second-step strategies that are most commonly recommended in consensus-based Practice Guidelines.

The most common starting medication used to treat patients with MDD is a serotonin reuptake inhibitor (SSRI). When the SSRI doesn’t yield a satisfactory response, the next most common steps are either to discontinue the SSRI and switch to a medication with a different mechanism of action, such as bupropion, or to continue the SSRI while adding another agent, commonly bupropion or a second generation antipsychotic, such as aripiprazole. Unfortunately, data assessing which of these approaches or specific medications is most effective or safe in either the short or long term is sparse, leaving physicians armed only with best guesses or “expert” consensus, rather than empirical evidence, to make these critical clinical decisions.
**Objectives:** The overall aim of VAST-D is to enhance treatment outcomes for representative outpatients diagnosed with nonpsychotic MDD and treated in primary or psychiatric VA care settings. In particular, VAST-D is designed to determine the comparative effectiveness of different treatment options for participants with MDD who fail to have a satisfactory outcome to treatment with their initial antidepressant. These options may be conceptualized as representing two overall treatment strategies: 1) **Medication Switch** — switching from the initial antidepressant to another antidepressant medication, **bupropion-SR** and 2) **Medication Augmentation** — augmenting the initial antidepressant with a second antidepressant, **bupropion-SR** or a second generation antipsychotic, **aripiprazole.** VAST-D's primary goal is to determine which of these 3 treatment alternatives is most likely to lead to remission. Other key objectives include comparisons of response, time to remission and response, relapse, anxiety symptoms, suicidal ideation and behaviors, side effects, tolerability, quality of life, health related costs and satisfaction with participation in the study. In general, we expect both augmentation strategies to be more effective than the switching strategy. In addition, VAST-D will have modest power (80%) to detect a 9 percent increase in remission between the 2 augmentation strategies. We expect augmentation with bupropion-SR to be better tolerated, have fewer important side effects and to be more cost effective than augmentation with aripiprazole.

**Research Plan:** VAST-D will randomize 1518 total patients (target of 51 participants at each of 30 to 35 participating sites) of both genders and all ethnic/racial and socioeconomic backgrounds. All patients will meet DSM-IV-TR criteria for nonpsychotic MDD. The diagnostic criteria for eligibility will be established by clinical interview supplemented with the 9-item Patient Health Questionnaire (PHQ-9). Final determination for eligibility will be made by the study clinician. Only participants with a suboptimal outcome to a well documented, adequately delivered (dose and duration), trial with a SSRI, a serotonin and norepinephrine reuptake inhibitor (SNRI) or the atypical antidepressant, mirtazapine, will be eligible for the study. Failure to achieve an adequate outcome will be ascertained by a QIDS-C16 ≥ 16 (considered severe depression) after at least 6 weeks of treatment or ≥ 11 (considered moderately severe depression) after at least 8 weeks of treatment. Otherwise, the inclusion criteria are broad and the exclusion criteria are few; participants with most comorbid general medical or psychiatric disorders are generally included to provide a broadly representative sample.
Participants will be randomized (1:1:1 ratio) to switch to bupropion-SR alone (BUP-SR) (n=506), current antidepressant plus bupropion-SR (antidep + BUP-SR) (n=506), or current antidepressant plus aripiprazole (antidep + ARI) (n=506). Treatment will be guided by clinician-rated symptom measures (the PHQ-9) and global side effects measures (the Frequency, Intensity, and Burden of Side Effects Rating or FIBSER) obtained at each treatment visit. Acute treatment visits will occur at baseline and at weeks 1, 2, 4, 6, 8, 10, and 12 to ensure delivery of appropriate and yet vigorous and tolerable pharmacotherapy. Participants who tolerate the acute treatment and achieve “adequate benefit” (QIDS-C16 ≤10) at 12 weeks will enter the 6-month Continuation Treatment, during which the initial treatment will continue and visits will occur every four weeks subsequently until patients have been followed for 36 weeks post-randomization. Neither the participant nor the treating clinician will be masked to treatment.

**Public Health Significance:** The public health impact of finding effective, safe, tolerable and cost efficient treatments of Veteran patients with MDD is indisputable. Currently, the majority of patients treated for MDD does not have satisfactory outcomes with their first antidepressant trial and are reliant on "next-step" regimens. Due to the paucity of data on the relative safety and efficacy of the most popular "next-step" strategies, selection between alternatives is often "hit or miss" and some of the most popular approaches for VA patients may have unforeseen, unfortunate, long-term consequences. If one of the strategies being tested in this study is found to produce greater remission rates, to have more sustained benefits and to be associated with fewer health-compromising side effects and health-related costs than the others, Veterans would receive better and less costly care for one of the most prevalent and disabling disorders they face. VAST-D results will provide an empirical basis for practice guidelines, replacing clinical consensus. With this large, multi-center, VA-based study, the VA would be a leader in improving the treatment guidelines for depression.
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I. INTRODUCTION AND BACKGROUND

A. Introduction

Major depressive disorder (MDD) is a chronic, recurring disease associated with increased risk of suicide and all-cause mortality, profound functional disability, and increased use of specialty mental health and general healthcare services. Though a broad range of treatments is available, recent large-scale studies have documented the failure of these treatments to achieve or sustain a state of symptomatic remission and functional recovery in many, if not most, patients. Our treatments usually get patients better but often not fully well, and are not optimally effective in preventing relapse. This disappointing state of affairs has resulted in the search for treatment strategies that might yield better outcomes.

More often than not, the initial antidepressant medication does not produce an optimal outcome, and the clinician is forced to move to “next-step” options. Once dose and duration of the antidepressant medication have been optimized, the two most commonly used "next-step" strategies for patients who fail to remit with an initial antidepressant trial are either augmenting with another agent or switching to another antidepressant. Because there is a paucity of systematically gathered data comparing the effectiveness of these two approaches, clinicians are left to base their treatment decisions on clinical hunches rather than evidence.

When the decision to augment with another agent is made, clinicians have minimal data-based guidelines to guide their selection of the most efficacious and safest treatment. Two of the most commonly used augmentation strategies are adding another antidepressant with a different mechanism of action than the first or adding a Second Generation Antipsychotic (SGA). Again, there are no published, randomized controlled trials yet available to help clinicians select between these two alternatives. In addition, although three SGAs have been FDA approved as augmentation agents for patients with treatment resistant depression data submitted in support of this indication tended to be short-term trials (6-week), placebo-controlled (with no active comparator), and very limited with respect to population diversity, and medical/psychiatric/substance abuse comorbidity. Despite these gaps in the evidence base, and despite the major public health concern with the adverse effects associated with the atypical
antipsychotics, this treatment approach is growing rapidly and has become the focus of mass media advertising directed towards both consumers and prescribers.

Thus, three major data gaps limit clinician's ability to select the most effective and safest "next-step" treatments for patients who fail to have an adequate antidepressant outcome: 1) no empirical comparisons of benefits and risks of switching vs. augmenting strategies, 2) no empirical comparisons of the benefits and risks of augmenting with another antidepressant compared to augmenting with a SGA, and 3) no empirical comparisons of the long term effectiveness and safety of SGAs and antidepressants.

In VAST-D we are proposing to fill these evidence gaps by addressing the safety and efficacy of three different "next step" treatments: two augmentation strategies (one that includes a SGA and one that does not), and one switching strategy. Efficacy, safety and cost-effectiveness are the major concerns of the proposed trial. Launching this study will allow the Veteran’s Health Administration to proactively establish effective and safe strategies for MDD and to lead the field in promulgating evidence-based treatments. We have assembled a Planning Committee of experienced investigators with strong track records in the design and completion of clinical trials in mental disorders in general and MDD in particular. This outstanding team has been brought together with the experienced resources of the appropriate VA Collaborating Centers. This process has resulted in the development of a clinical trial protocol that is focused, efficient, and important. Its results will set the standard for the field for years to come.

B. Study Rationale

Major depressive disorder (MDD) is a serious, debilitating, life-shortening illness that affects approximately 13 to 14 million adults of all ages and backgrounds in the US (6.6% of the population in a given year (Kessler, Berglund et al. 2003). Most depressed patients have a recurrent or chronic course with either prolonged episodes or substantial interepisode symptomatology and disability (Keller 2001; Rush, Trivedi et al. 2006). MDD is the 4th leading cause of death with about 15% of individuals with severe MDD dying by suicide (APA 2000). MDD is also the leading cause of disability in the U.S. for ages 15-44 (Kessler, Berglund et al. 2003) with total costs to society in excess of $80 billion annually. Approximately two-thirds of
these costs reflect the enormous disability associated with MDD, with the remainder due to direct medical costs of treatment, increased utilization of health care services for general medical conditions by MDD patients, or the loss of life through suicide (Greenberg, Scharf et al. 1993; Birnbaum, Leong et al. 2003; Greenberg, Kessler et al. 2003; Kessler, Berglund et al. 2003). Suicide, the most dire consequence of MDD, is an alarmingly prevalent cause of death around the world, and increasingly so among both active duty military and Veterans (Kaplan, Huguet et al. 2007; Kaplan, McFarland et al. 2009). US Secretary of VA Shinseki has reported that of the more than 30,000 suicides each year in America, about 20 percent are committed by Veterans (Carda 2010) and the relative rates of suicides in the military and Veteran population are increasing compared to non-Veteran populations (Kaplan, McFarland et al. 2009). In turn, suicide is directly linked to high rates of untreated and/or inadequately treated MDD (Isacsson, Bergman et al. 1996; Rihmer 2001; Isacsson, Holmgren et al. 2009) and the best known prevention is timely and effective treatment of depression (Mann, Apter et al. 2005).

The burden of depression is at least as great in Veterans as in the general population. A recent study found that in FY 2007, 191,522 VA patients were diagnosed with treatment resistant MDD, amounting to 13% of all patients diagnosed with mental illness (Mohamed, Leslie et al. 2009). Over half (51%) received service-connected disability compensation, reflecting substantial dysfunction. Additionally, a recent phone survey found 14% of Veterans of Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) met criteria for MDD, about equal to the proportion diagnosed with post-traumatic stress disorder (PTSD) (Tanielian, Jaycox et al. 2008). In FY 2007, 15% OIF/OEF Veterans who used VA mental health services were diagnosed with MDD (unpublished data, Northeast Program Evaluation Center [NEPEC]). In light of these findings, the demand for treatment of MDD in VA, already quite substantial, is likely to increase significantly in the coming years and **effective treatment of MDD is a major VHA priority**.

In dollar terms, the costs associated with treatment of MDD in VA are substantial. The cost of inpatient and outpatient mental health services for the 191,000 Veterans identified above are estimated to be $3,530 annually per Veteran; with the cost of antidepressant medications estimated to be $548 annually per Veteran, the total annual psychiatric cost comes to $4,068 per
Veteran. This comes to a total VA cost of $780 million, about one-fourth of the entire annual VA mental health budget. When the costs of associated medical co-morbidity and accompanying general medical expenditures are added, the resultant expenditures are staggering (Henk, Katzelnick et al. 1996; Druss and Rosenheck 1999).

A key reason for the high costs of MDD is the length of time it takes for patients with MDD to recover from a single major depressive episode. Less than one-third of patients remit to the first trial of an antidepressant medication within 12-14 weeks of treatment, even with enhanced resources (Trivedi, Rush et al. 2006). Finding an effective antidepressant treatment regimen for the two-thirds of patients who do not remit remains a daunting challenge for many patients and physicians. The current best practice when the initial monotherapy fails is either switching to another antidepressant or adding a second treatment to the first medication (called augmentation when adding a non-antidepressant, and combination when adding a second antidepressant). For purposes of simplicity, we will refer to both "add-on" conditions as "augmentation" throughout this proposal. Because there are a few, if any, data based guidelines to inform prescribers when to switch or augment, or which agent is most likely to work best for an individual patient as an augmentation treatment, decisions are based more on “expert opinions” than on empirical evidence. The current “trial and error” process can involve months of waiting for significant relief from depressive symptoms (Rush, Trivedi et al. 2003). The proposed study will be the first to systematically compare benefits and risks of 3 commonly used switch and augmentation strategies for patients with MDD who fail to remit after an adequate antidepressant trial: switching to Bupropion-SR (BUP-SR) vs. augmenting with BUP-SR vs. augmenting with aripiprazole (ARI).

C. Goals of Treatment: Achieving and Maintaining Remission

C.1. Aiming for remission

It is now well accepted that the goal of acute antidepressant treatment is remission, defined qualitatively as “close” to asymptomatic status and quantitatively as a sustained Quick Inventory of Depressive Symptoms (QIDS-C16) total score of ≤5. Achieving and sustaining symptomatic remission is the first crucial step towards functional recovery. Failure to achieve remission is associated with continued suffering, impaired functioning and quality of life, medical morbidity,
risk for suicide and rapid relapse and recurrence (Murphy, Monson et al. 1987; Judd, Akiskal et al. 1997; Miller, Keitner et al. 1998; Judd, Paulus et al. 2000). Yet it is abundantly clear that about 2 out of every 3 patients treated for major depression will not achieve remission with the first antidepressant prescribed (Trivedi, Fava et al. 2006). Thus, a compelling public health priority is developing effective and safe “next-step” strategies for patients with MDD who fail to achieve remission with the initial antidepressant trial. This proposed trial addresses that need.

The most commonly used strategies for patients who fail to remit to an adequately delivered SSRI trial are switching to another antidepressant with a different mechanism of action, such as BUP-SR (Fredman, Fava et al. 2000), augmenting with another antidepressant, more often than not BUP-SR (Zisook, Rush et al. 2006), or augmenting with a SGAs, such as aripiprazole (Papakostas 2009). Theoretical advantages of switching are its simplicity, safety, minimization of side effects and the possibility of being relatively inexpensive. Theoretical advantages of augmentation strategies are that they build on the effectiveness of the initial medication and avoid the loss of already achieved benefits. By avoiding the potential disruptive effect of withdrawal and cross-titration, therapeutic benefits may be more rapid than switching. Augmentation provides potential additive pharmacological effects by affecting a broad range of neurotransmitters and/or by creating a broad spectrum of action. A well selected augmenting agent may also help reduce specific residual symptoms, such as fatigue or insomnia, or target specific side effects of the original antidepressant such as weight gain or sexual dysfunction.

In practice, clinicians often choose switching for patients with minimal response and/or troublesome side effects and augmenting for patients with moderate response and few side effects. However, choosing between these strategies in fact is more a matter of opinion or even guesswork than solid, evidence-based rational decision making, as few studies have directly compared switching vs. augmenting strategies and no published studies have directly compared combining with antidepressants (e.g., adding BUP-SR) vs. augmenting with a SGA (e.g., adding aripiprazole). This proposed study directly compares switching to BUP-SR to augmenting with BUP-SR and to augmenting with aripiprazole and compares combining with BUP-SR and to augmenting with aripiprazole.
C.2. Maintaining remission/preventing relapse

Depression is a chronic and/or recurring disorder (Keller 2001; Rush 2007)). Thus, it is not enough to get a depressed person well, it is equally important to keep them well. The goal of continuation treatment, the time period between initial remissions of symptoms to “recovery” from the episode (Rapaport 2009), is to maintain remission and prevent relapse. Most “next step” or treatment resistant studies, generally between 6-12 weeks in duration, have focused only on acute treatment, leaving open the questions of how best to maintain remission, prevent relapse or maximize long term tolerability and safety. There is no randomized, controlled trial evidence to guide selecting among potential monotherapy, combination or augmentation agents to prevent relapse/recurrence. We also do not know whether treatments that are more effective in the short term will also be associated with more consistent, better longer-term symptom control, tolerability or safety. This may be particularly important for depressed patients treated with atypical antipsychotics, medications known to be associated with long term health problems, such as weight gain, metabolic syndrome and neurological side effects (Wirshing, Spellberg et al. 1998; Allison, Mentore et al. 1999; Kraus, Haack et al. 1999; Allison and Casey 2001; Newcomer 2007). If two possible “next step” choices are equally effective, but one is not well tolerated and caused weight gain, metabolic syndrome and/or tardive dyskinesia, while the other is well tolerated and relatively safe, the second would clearly be the treatment of choice. This proposed study goes beyond acute treatment effects by further comparing them during a 24-week continuation phase in which effectiveness, tolerability, safety and costs of the three different treatments are assessed.

C.3. Lessons Learned and Not Learned from Sequenced Treatment Alternatives to Relieve Depression: (STAR*D and CO-MED)

STAR*D, an ambitious and ground breaking clinical trial, was designed to determine the most effective and well tolerated “next steps” for patients failing to achieve remission to initial treatment with an SSRI, and to subsequent failed treatments, found that a very disappointing two out of three patients with nonpsychotic major depression do not remit with an initial, well delivered 12-14 weeks SSRI trial. In addition 16% fail even to tolerate an adequate dose (Rush, Trivedi et al. 2006; Zisook, Ganadjian et al. 2008). For such non-remitters, combining an antidepressant with BUP-SR was more effective and well tolerated than augmenting with
buspirone on some, but not all measures, yielding a remission rate of 39%. Augmenting with BUP-SR was equally effective as augmenting with sertraline or venlafaxine (remission rates of 26%, 27% and 25% respectively). Over 1-year follow up, 55% of patients relapsed, with significantly higher relapse rates for patients who did not achieve remission prior to entering the follow-up period. Because of a unique methodology that allowed participants to opt out of certain randomizations, too few participants accepted the possibility of being randomized to either switching vs. augmenting medication options. Therefore, STAR*D failed to provide comparative information on the effectiveness, safety or costs of switching vs. augmenting. *The proposed study is designed to uncover the relative effectiveness and safety of common switching and augmenting strategies.*

Additional levels of treatment in STAR*D compared various other switching and augmenting strategies. However, one treatment that was **not** studied was augmenting with an atypical antipsychotic, in part because this was not as widespread a practice when STAR*D was being designed as it is now, largely because none of the atypical antipsychotics were yet approved for marketing by the FDA as augmentation agents for major depression and partly because of concerns of long term safety and costs. However, in more recent years, several studies have suggested short term efficacy of atypical antipsychotics as compared to placebo in refractory MDD. Two medications in this class have been approved for augmentation of antidepressants in depressed patients and these medications, aripiprazole and quetiapine, have become among the most prescribed agents for patients with major depression nationally including in the Veterans Health Administration (DeBattista and Hawkins 2009; Mohamed, Leslie et al. 2009). But this widespread use has proceeded data supporting their long term effectiveness, safety or costs. *The proposed study is designed to provide both acute and continuation phase treatment data on the effectiveness, tolerability and safety of a frequently prescribed but dramatically under-studied medication, the atypical antipsychotic, aripiprazole.*

Recently published findings from the CO-MED study (Rush, Trivedi et al. 2011) suggest that combination antidepressant treatment is no more efficacious than monotherapy in MDD. Short-term (12 week) and longer-term (7 month) rates of response and remission were roughly equal in
a sample of 665 outpatients with at least moderately severe nonpsychotic chronic or recurrent MDD. This study differs from CO-MED in a number of important ways:

1. The CO-MED sample was not selected on the basis of inadequate response to earlier or ongoing treatment,

2. Antipsychotic augmentation was not offered,

3. The population was typical of community samples: 2/3 women; low rates of alcohol (10%) and drug abuse (5%); 2/3 with 0-1 comorbid Axis I disorders and quite different from a VA population,

4. There are contradictory findings in the field (e.g. Blier P et al Neuropsychopharmacol 2009; Am J Psychiatry 2010).

D. Why BUP-SR?
BUP-SR was initially developed from a targeted program designed to produce an antidepressant with a unique pharmacologic profile to improve the safety and tolerability of existing antidepressants (Soroko and Maxwell 1983). BUP-SR is the only antidepressant available with a dual neurotransmitter systems improving neurotransmission of both norepinephrine and dopamine. It is widely used to augment SSRI or SNRI effectiveness and help relieve or reverse certain adverse events associated with these agents (Stahl, Pradko et al. 2004; Zisook, Rush et al. 2006). In a survey of 801 clinicians responding to a question regarding the best strategy for patients not responding to an SSRI, BUP-SR was the most widely chosen augmenting and switching agent (Mischoulon, Nierenberg et al. 2000). Figure 1 below from the VA Serious Mental Illness Treatment Research and Education Center (SMITREC) shows the use of bupropion among Veterans diagnosed with MDD between FY 00 and FY 09. Although the use of bupropion has increased in recent years, the overwhelming majority of patients with MDD is not receiving bupropion and thus will be eligible for this trial.
Long-term efficacy and tolerability were demonstrated in a 1-year relapse-prevention study in which patients who had responded to 8 weeks of therapy with BUP-SR were randomly assigned in a double-blind manner to either continue therapy with active medication or switch to placebo (Weihs, Houser et al. 2002). The odds of relapsing for subjects in the placebo group were almost twice that seen in subjects in the BUP-SR group and the median time to relapse was greater than 44 weeks for BUP-SR compared to 24 weeks for placebo, demonstrating good long term effectiveness.

Switching to BUP-SR is a commonly used (Fredman, Fava et al. 2000) and effective treatment strategy for patients who do not respond to a trial of a serotonin reuptake inhibitor (SSRI) (Fava, Papakostas et al. 2003). In the "switching" arm of the STAR*D study (Rush, Trivedi et al. 2006) patients who did not respond to citalopram were randomly assigned to receive either BUP-SR, sertraline, or extended-release venlafaxine. These treatments did not differ significantly with
respect to outcomes, tolerability, or adverse events. Remission rates were about 25% for each of the three treatments.

Augmenting antidepressants with BUP-SR also has become an increasingly common and effective strategy in the treatment of resistant depression (Bodkin, Lasser et al. 1997; Spier 1998; DeBattista, Solvason et al. 2003; Lam, Hossie et al. 2004). In STAR*D, augmenting citalopram non-remitters with BUP-SR resulted in similar remission rates as buspirone but in a statistically and clinically greater reduction in depression severity and a lower dropout rate due to intolerance (Trivedi, Rush et al. 2006). Overall, 39% of patients augmented with BUP-SR remitted and only 13% were intolerant to it.

BUP-SR was selected for this study as the antidepressant combination to test against aripiprazole on the basis of its proven efficacy, wide use, relatively acceptable cost and low side effect burden. It is among the least likely antidepressants to cause sedation, weight gain or sexual side effects and is effective for a broad spectrum of patients with MDD, including those with atypical, melancholic and anxious features (Thase, Haight et al. 2005; Zimmerman, Posternak et al. 2005). It was selected as the "switching" antidepressant for similar reasons and also as an ideal agent to examine augmentation vs. switching tactics since it allows direct comparison of augmenting and switching with the same agent.

E. Why aripiprazole?

Atypical antipsychotics are increasingly being used as augmenting strategies in the treatment of depression. Aripiprazole, effective in combination with many antidepressants, was the first atypical antipsychotic approved by the US Food and Drug Administration (FDA) for adjunctive use in patients not fully responding to antidepressants (Patkar, Peindl et al. 2006; Berman, Marcus et al. 2007; Pae, Patkar et al. 2007; Hellerstein, Batchelder et al. 2008; Marcus, McQuade et al. 2008). Next, olanzapine, in combination with fluoxetine, received FDA approval for use in treating depression. More recently, quetiapine has received FDA approval for this same indication. Studies have shown positive evidence of the efficacy of antipsychotics as augmenting agents in refractory MDD both in uncontrolled studies and in short term controlled trials (Ostroff and Nelson 1999; Shelton, Tollefson et al. 2001; Adson, Kushner et al. 2004; Papakostas, Petersen et al. 2004; Worthington, Kinrys et al. 2005). A recent meta-analysis of
randomized clinical trials found that antipsychotic augmentation for MDD resulted in greater remission and response rates than adjunctive placebo treatment, with remission rates of 47.4% versus 22.3% (Papakostas, Shelton et al. 2007).

In the year prior to the approval of aripiprazole for MDD, 20% of VA patients diagnosed with MDD received antipsychotics, exclusive of those who were diagnosed with either schizophrenia or bipolar disease, the principal approved indications for antipsychotic medications (Mohamed, Leslie et al. 2009). Following FDA approval, advertisements for atypical antipsychotics for MDD have begun to appear in major psychiatric journals as well as on TV and in the popular media, along with announcements for special educational events, dinners and symposia on the treatment of MDD sponsored by pharmaceutical companies and there has thus been a notable increase in inclination among clinicians to use it for MDD (Mojtabai and Olfson 2010). Data from the VA Serious Mental Illness Treatment Resource and Evaluation Center (SMITREC) also showed considerable increase in recent years in the use of atypical antipsychotics among patients diagnosed with MDD, particularly for aripiprazole. Figure 2 below shows the use of SGAs among Veterans diagnosed with MDD between FY 00 and FY 09.
Despite their wide-spread use for patients with MDD, long-term improvements in remission rates, relapse prevention, long-term tolerability and safety and the cost-effectiveness of antipsychotic augmentation have yet to be investigated (Rapaport, Gharabawi et al. 2006; Berman, Marcus et al. 2007; Bender 2008). Further, most of the published studies have been done on highly selective patients with minimal medical, alcohol and drug co-morbidities, perhaps not representative of "real" patients seen in most VAs. As a class, the atypical antipsychotics have been associated with a number of severe treatment emergent effects, including death in certain populations (Correll, Frederickson et al. 2006; Correll, Frederickson et al. 2007). This risk may be especially important in patients with MDD as several studies have shown increased mortality in patients with MDD (Cuijpers and Schoevers 2004), often linked to the risk of heart disease (Frasure-Smith and Lesperance 2005) and more specifically by VA researchers VA (Whooley 2006). Both antidepressants and atypical antipsychotics are known to be associated with weight gain, which is not only associated with increased cardiovascular risk but can also contribute to poor medication compliance (Fava 2000; Taylor and McAskill 2000;
Allison and Casey 2001). Increased metabolic risk associated with long term use of many atypical antipsychotics (Wirshing, Spellberg et al. 1998; Allison, Mentore et al. 1999; Kraus, Haack et al. 1999; Allison and Casey 2001; Newcomer 2007) may thus be especially hazardous for Veterans with MDD (Newcomer 2005). Longer term information on the metabolic risk associated with aripiprazole in MDD is limited. Additionally, the risk of extra pyramidal syndromes, tardive dyskinesia, and hyperprolactinemia, not uncommon with atypical antipsychotics, has yet to be carefully examined, although some studies show increased TD risk in people with affective disorders (Woods, Saksa et al. under review).

Aripiprazole was selected for this study because as the first FDA approved augmenting atypical antipsychotic, the potential for its substantial and increasing use for patients with depression is great. Additionally, aripiprazole has potentially favorable long-term side effect profile relative to other medications in its class (Potkin, Saha et al. 2003; Swainston Harrison and Perry 2004). Aripiprazole has a lower risk of metabolic side effects—at least during short-term treatment—than does the olanzapine-fluoxetine (Newcomer 2005), but aripiprazole does have some other particularly troublesome adverse effects, such as akathisia and restlessness (Marcus, McQuade et al. 2008). Given the increasing use of aripiprazole and its relatives, the paucity of data on its long-term benefits and risks in patients with MDD, and the potential for serious harm, a well-designed study of its short and long term effectiveness and costs in real patients with MDD is a clinical and public health imperative.

F. Summary
The proposed study has been designed to address pivotal questions that are essential to answer in order to improve treatment outcomes for patients with major depression. In patients with MDD who fail to achieve remission with SSRI, SNRI or mirtazapine monotherapy: 1) Is switching medications (e.g., to BUP-SR) as effective in both the short run and longer-term as augmenting with antidepressants (e.g., with BUP-SR) or with atypical antipsychotics (e.g., with aripiprazole)? 2) Is augmenting with atypical antipsychotics (e.g., with aripiprazole) as effective in both the short run and longer-term as augmenting with antidepressants (e.g., with BUP-SR)? 3) Is augmenting with aripiprazole as safe, tolerable and cost-effective in the short term and longer term as either augmenting with BUP-SR or switching to BUP-SR? This large multi-site VA study is designed to provide definitive answers to these vital questions.
II. PRELIMINARY RESEARCH

Preliminary pharmacoepidemiologic research used national data on all antipsychotic prescriptions provided to Veterans who received a diagnosis of MDD (ICD-9 criteria) without a comorbid diagnosis of schizophrenia or schizoaffective disorder or bipolar disorder in the Department of Veterans Affairs (VA) health care system in fiscal year 2007 (Mohamed, Leslie et al. 2009). We identified the rates of use of antipsychotics in MDD during the period just prior to FDA approval of the first SGA for this purpose, and examined the proportion of patients who received antipsychotic medication at doses below those recommended by the schizophrenia Patient Outcomes Research Team (PORT) guidelines for antipsychotic therapy of schizophrenia doses (Lehman, Kreyenbuhl et al. 2004) that would appear to be appropriate for treatment of MDD. This data showed that in 2007 only 20.6% of Veterans with MDD received antipsychotic medications. These data suggested that with the advent of FDA approval of SGAs as an adjunctive treatment, and the initiation of aggressive marketing based on short-term registration trials, there was a substantial potential for extensive and costly expansion in the use of these agents across VAs. Further research, we concluded, is desperately needed to evaluate the long-term safety, efficacy and cost-effectiveness of these medications and this conclusion led directly to the development of the proposal for the current study.

A second study (Leslie, Mohamed et al. 2009) confirmed the widespread off-label use of antipsychotics in VA for other illnesses in addition to MDD. That study demonstrated that well over half of all use of these agents is for non-psychotic disorders. This proposed study will be the first to investigate the value of antipsychotics against other treatments in non-psychotic disorders in VA populations and thus establishes an important precedent for the rigorous comparative effectiveness evaluation of the use of antipsychotics in disorders in which they are commonly prescribed but for which industry is not likely to conduct needed long term evaluations of benefits, risks and cost-effectiveness. The proposed study thus has important specific relevance to the case of MDD and broader significance for the study of use of antipsychotic drugs in non-psychotic disorders.
III. STUDY OBJECTIVES

A. Primary Objectives
The primary objective is to compare the acute (up to 12 weeks) treatment effectiveness of either augmenting an antidepressant with aripiprazole (antidep + ARI) or augmenting an antidepressant with BUP-SR (antidep + BUP-SR) vs. switching to BUP-SR- monotherapy (BUP-SR) based on symptom remission rates as measured by achieving a score of ≤ 5 on the QIDS-C16 for 2 consecutive visits in Veterans with a Major Depressive Disorder (MDD) who have not achieved optimal response after an adequate trial on antidepressant monotherapy.

Primary Hypotheses

Hypothesis 1.a.: Remission rate from MDD will be higher in patients whose treatment is augmented with BUP-SR (antidep + BUP-SR) compared to those switched to BUP-SR monotherapy.

Hypothesis 1.b.: Remission rate from MDD will be higher in patients whose treatment is augmented with aripiprazole (antidep + ARI) compared to those switched to BUP-SR monotherapy.

B. Secondary Objectives
The secondary objectives are to compare the acute (up to 12 weeks) and long term (up to 36 weeks) effectiveness, safety, costs and cost-effectiveness of augmenting an antidepressant with aripiprazole (antidep + ARI) vs. augmenting an antidepressant with BUP-SR (antidep + BUP-SR) vs. switching an antidepressant to BUP-SR monotherapy. Effectiveness is assessed by remission rates and relapse rates (defined as a QIDS-C16 score of ≥ 11 after remission has been achieved or after the participant has entered the continuation phase of the study); safety is assessed by side effects, tolerability and discontinuation; costs are assessed by costs of care and health care utilization; and cost-effectiveness is assessed by the ratio of costs to quality-adjusted life years.
**Secondary Hypotheses**

**Hypothesis 2.a.:** Remission rate will be greater in patients whose treatment is augmented with BUP-SR (antidep + BUP-SR) than in those augmented with ARI (antidep + ARI).

**Hypothesis 2.b.:** Relapse rate (within 36 weeks of the initiation of treatment) will be lower in patients whose antidepressant is augmented with BUP-SR (antidep + BUP-SR) than in those whose antidepressant is switched to BUP-SR monotherapy.

**Hypothesis 2.c:** Relapse rate (within 36 weeks of the initiation of treatment) will be lower in patients whose treatment is augmented with aripiprazole (antidep + ARI) vs. those switched to BUP-SR monotherapy.

**Hypothesis 2.d:** Relapse rate (within 36 weeks of the initiation of treatment) will be lower in patients whose treatment is augmented with BUP-SR (antidep + BUP-SR) than in patients whose treatment was augmented with ARI (antidep + ARI).

**Hypothesis 2.f:** The proportion of patients who develop akathisia, other akathisia-like side effects (e.g., tremor, irritability, motor restlessness) and extrapyramidal side effects will be greater in the patients whose antidepressant treatment is augmented with ARI (antidep + ARI) compared to patients whose treatment is augmented with BUP-SR (antidep + BUP-SR), or switched to BUP-SR monotherapy (BUP-SR).

**Hypothesis 2.g:** The relative costs (direct and indirect) of augmenting an antidepressant with aripiprazole (antidep + ARI) will be greater than the costs of antidepressant augmentation with BUP-SR (antidep + BUP-SR), and the costs of antidepressant augmentation with BUP-SR (antidep + BUP-SR) will be greater than the costs of switching to BUP-SR monotherapy. Augmentation and monotherapy with BUP-SR will be more cost-effective than ARI augmentation.
C. Tertiary (Other) Objectives

**Tertiary Objective 1:** To compare response (as opposed to remission) among Veterans treated with an antidepressant and aripiprazole (antidep + ARI) vs. an antidepressant and BUP-SR (antidep+ BUP-SR), and to compare the response to the augmentation regimens with response to switching to BUP-SR monotherapy (BUP-SR) where response is defined as ≥50% reduction in symptoms severity as measured by the 16-item QIDS-C16.

**Tertiary Objective 2:** To compare change in depression symptoms (as measured by the mean percent change in the QIDS-C16 from baseline to the end of acute treatment) among Veterans treated with an antidepressant and aripiprazole (antidep+ ARI) with those treated with an antidepressant and BUP-SR (antidep+ BUP-SR), and to compare the change in depression symptoms in patients receiving the augmentation regimens with those switched to BUP-SR monotherapy (BUP-SR).

**Tertiary Objective 3:** The proportion of patients who discontinue treatment due to lack of tolerability will be greater in patients whose antidepressant treatment is augmented with ARI (antidep + ARI) vs. patients whose treatment is augmented with BUP-SR (antidep+ BUP-SR), and will be greater in patients whose antidepressant treatment was augmented with BUP-SR (antidep+ BUP-SR) compared to those switching to BUP-SR monotherapy.

**Tertiary Objective 4:** To compare Acute Phase outcomes to treatment among the three regimens in terms of other associated features of depression (e.g., anxiety and suicidal ideation); function; quality of life; attrition due to side effects; overall side-effect burden; extrapyramidal symptoms and other specific side effects, such as BMI or akathisia.

**Tertiary Objective 5:** To compare Long-Term outcomes to treatment among the three regimens in terms of a change in associated features (e.g., anxiety and suicidal ideation); function; quality of life; attrition due to side effects; overall side-effect burden; extrapyramidal symptoms and other specific side effects, such as BMI or akathisia.
IV. STUDY OUTCOME MEASURES

A. Primary Outcome

The primary outcome for this study is remission rate during the acute treatment phase. Remission is defined as “close” to asymptomatic status and operationalized as a sustained Quick Inventory of Depressive Symptoms (QIDS-C16) of ≤5 for two consecutive visits. As in many areas of medicine, there is no biological or physiological parameter than can be used to assess outcomes of treatment of depression. Outcomes assessments rely on patient reports of symptoms. These individual reports can be used as is in a self-rated scale or they can be provided to a clinician to assess in a clinician-rated scale. In VAST-D, we propose to use both self-rated (PHQ-9) and clinician-rated (QIDS-C16) assessments; the PHQ-9 to guide treatment and dosing strategy and the QIDS-C16 to assess outcomes. There are alternative ways to approach outcome assessments. In the section below we discuss the rationale for our choice of this combined approach.

The QIDS is rapidly becoming the “gold standard” for depression intervention trials. QIDS is psychometrically sound, can be accurately assessed for virtually all patients, and is economically feasible and clinically meaningful. Sensitivity of the QIDS is equivalent to the more detailed 30-item Inventory of Depressive Symptomatology, Clinician-Rated (IDS-C) (Trivedi, Rush et al. 2004), the Hamilton Depression Rating Scale (Ham-D or HDRS) (Rush, Bernstein et al. 2006) (Rush, Fava et al. 2004) and the Montgomery-Asberg Depression Rating Scale (MADRS) (Doraiswamy et al, 2010). Like the PHQ-9, the QIDS-C16 provides ratings for each of the 9 symptoms used by the DSM-IV-TR to characterize MDD, but it provides a richer array of associated phenomena and is more finely nuanced than the PHQ-9 (Trivedi 2009).

In VAST-D, the QIDS-C16 will be assessed by a research assistant trained and certified in QIDS-C16 assessment and masked to treatment assignment. It is important to remember that in order to enhance feasibility and maximize applicability of findings to “real” clinical settings, neither the participant nor clinician will be masked to treatment.
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ATHF = Antidepressant Treatment History Form
AO = Adherence Questionnaire
ASES = Arizona Sexual Experience Scale
BAI = Beck Anxiety Inventory
BAS = Barnes Akathisia Scale
BCDF = Baseline Clinical and Demographic Form
CGI-I = Clinical Global Impression - Improvement
CGI-S = Clinical Global Impression - Severity
CIRS = Cumulative Illness Rating Scale
CMT = Concomitant Medication Tracking form
C-SSRS = Columbia Suicide Severity Rating Scale
ACE = Adverse Childhood Experiences
AQ = Adherence Questionnaire
ATFH = Antidepressant Treatment History Form
BL = Baseline
PCL-5 = PTSD Checklist for DSM-5 (administered if PTSD diagnosis per MINI)
QIDS-C_16 = 16-item Quick Inventory of Depressive Symptomatology - Clinician-report
Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire
RX = Study Medication Tracking form
SE = Side Effect Checklist
VS = Vital Signs (BP, P, weight)
WSAS = Work and Social Adjustment Scale
FIBSER = Frequency, Intensity, and Burden of Side Effects Rating
AE/SAE = Adverse Event / Serious Adverse Event Form (as needed)
CSP#576 (VAST-D) Protocol Version 5.2 35 03/09/2015

*End of Acute Treatment Assessment  **End of Continuation Treatment/End of Study
***Depression, Eating Disorder, Bipolar, PTSD, Substance Use and Psychosis modules
B. Secondary Outcomes

In addition to remission rates, the QIDS-C16 allows assessment of other secondary outcomes, such as response (reduction in QIDS-C16 of $\geq 50\%$), percentage symptomatic improvement and relapse (QIDS-C16 $\geq 11$ after remission or during continuation treatment). Several additional outcome measures, assessing suicidal ideation and behaviors, anxiety, global improvement, side effects, quality of life, health related costs, adherence and satisfaction also will be collected. These include:

B.1. Suicidal Ideation and Behaviors
The Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner, Melvin et al. 2007) will be used to detect and measure the current intensity of the patients' specific attitudes, behaviors, and plans to attempt suicide. The C-SSRS will be administered at baseline, at end of acute treatment, at 24 weeks, and at end of study. For all other visits, item 12 of the QIDS-C16 will be used to assess suicidal thoughts and behaviors. A score of 3 on the QIDS-C16 item 12 will trigger an administration of the more comprehensive C-SSRS.

B.2. Anxiety
The Beck Anxiety Inventory (BAI) (Beck, Epstein et al. 1988) will be used to measure the severity of anxiety symptoms. The BAI will be administered at baseline, at end of acute treatment, at 24 weeks, and at end of study.

The PTSD Checklist for DSM-5 (PCL-5) is a 20-item measure corresponding to the DSM-5 symptom criteria for PTSD and takes 5-10 minutes to complete. The PCL will be administered at baseline, at end of acute treatment, at 24 weeks, and at end of study. At the time of the first PCL-5 assessment, participants with PTSD will also be asked to answer a few questions about exposures to stressful events (while in the military or otherwise) and about the most stressful event, i.e., the event that currently bothers the participant the most.

B.3. Clinical Global Impression
The Clinical Global Impression Scale (CGI) (Guy 1976) consists of two global ratings. The first, Clinical Global Impressions-Severity Scale (CGI-S) assesses the evaluator’s impression of the
patient’s current illness severity. Scores range from 1 = not ill at all through 7 = among the most extremely ill. The second, the **Clinical Global Impressions-Improvement Scale (CGI-I)** is a single scale rating scores range from 1 (very much improved) through to 7 (very much worse) and will also be used to track change in general symptoms over time. The CGI-S will be administered by the Independent Evaluator (along with the QIDS-C16) at all visits and the CGI-I at all post-baseline visits.

**B.4. Side Effects**
The patient-rated **Frequency and Intensity of Side Effects Rating/Global Rating of Side-Effect Burden (FIBSER)** which are seven-point Likert scales developed for the STAR*D study (Wisniewski, Rush et al. 2006) also will be administered at each visit.

General side effects will be assessed at baseline and at each follow-up visit utilizing a checklist for possible side effects based on **Systematic Assessment for Treatment of Emergent Events – Specific Inquiry (SAFTEE-SI)**. The items on the checklist include the most commonly reported side effects of antidepressant medications.

**B.5. Weight** and **vital signs** will also be measured at baseline and at each subsequent study visit. **Laboratory** assessments and other **metabolic indicators**, such as waist circumference, fasting plasma lipids (total, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol, and triglycerides, fasting plasma glucose, and BP, as recommended by the American Heart Association, will be measured at baseline, at end of acute treatment (12 weeks) , at 24 weeks and at the end of the study. A **pregnancy test** will be administered to all women of child-bearing age during screening. Women who are pregnant will not be randomized.

**B.6. Antipsychotics’ motor side effects** will be assessed for all patients with scales in which higher scores uniformly indicate more serious problems: The **Barnes Scale for Akathisia (BAS)** (Barnes 1989) (possible range= 0-14) . These will be measured at baseline, at end of acute treatment, at 24 weeks, and at the end of the study. In addition, the symptoms: tardive dyskinesia, pseudoparkinsonism and dystonia will be prompted for at each follow-up visit.
B.7. The Mania / Hypomania Questionnaire will be administered at baseline, at end of acute treatment, at 24 weeks, and at the end of the study to assess the occurrence of the proposed DSM-5 ‘mixed state’ features that are associated with MDD and with poor outcomes to traditional antidepressant medications. The DSM-5 Mood Disorders Task Force proposes to include mixed states as a subtype of Major Depressive Disorder (MDD). Including this instrument will help us understand the contribution of hypomanic/manic symptoms on response and tolerability of antidepressant and antipsychotic-augmented treatment for resistant MDD.

B.8. The Arizona Sexual Experience Scale (ASES) (McGahuey, Gelenberg et al. 1997) will be used to specifically measure sexual side effects at baseline, at end of acute treatment, at 24 weeks, and at the end of the study.

B.9. Depression-Specific Quality of Life A major goal of treatment is improvement in day-to-day work and interpersonal function. The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF) (Endicott, Nee et al. 1993) is designed to measure satisfaction and enjoyment, as opposed to function per se, in various domains: physical health, mood, work, household duties, school/course work, leisure time activities, social relations, and general activities. The short version of the Q-LES-Q has 16 items, and is obtained in 6 minutes. This instrument is more sensitive to small changes in depression than general quality of life measures and will be administered at baseline, at end of acute treatment, at 24 weeks, and at the end of the study. In addition, at the same time points, a 7-item Positive Mental Health Questionnaire will be administered just after the self-rated PHQ-9 s to record the participant’s self-rated responses (about 1 minute) to additional measures of positive mental health, functioning and return to usual self.

B.10. Cost Effectiveness and Health Economics
As a measure of the participant’s utility levels, the EuroQoL (EQ-5D) Scale, which measures health-related quality of life, will be administered at baseline, at end of acute treatment and at the end of the study. The EQ-5D is a survey of 5 questions that will be self administered. It assesses health related quality of life in 3 domains: mobility, physical activity and social activity. The EQ-5D has been found to be significantly associated with both cross-sectional and longitudinal depression severity (Sapin, Fantino et al. 2004). In addition, an income and employment
questionnaire, the Work Productivity and Activity Impairment scale (WPAI), and the Work and Social Adjustment Scale (WSAS) will be administered at baseline, at end of acute treatment, at 24 weeks, and at the end of the study to measure income, employment, and social adjustment. Data also will be collected regarding use of both VA and non-VA resources.

B.11. Retention and Compliance
Retention will be measured through a survival analysis of the number of days to discontinuation of randomly assigned treatment. This measure was selected as the primary outcome in the NIMH-funded CATIE study of atypical antipsychotics in treatment of schizophrenia and Alzheimer’s disease (Schneider, Tariot et al. 2001; Stroup, McEvoy et al. 2003). Self-reported medication compliance will be also recorded at each follow-up visit. Although use of Micro-Electronic Monitoring Systems (MEMS) is the state of the art approach to measuring medication compliance, MEMS will not be feasible in this study because standard VA prescriptions uniformly cover 90 days and are mailed, making it difficult to assure that the MEMS would be used properly. We have also decided against pill counts because this method has been demonstrated in several studies to be unreliable (Pullar, Birtwell et al. 1988; Rudd, Byyny et al. 1988; Pullar, Kumar et al. 1989; Lee, Kusek et al. 1996; Grymonpre, Didur et al. 1998). In a recent trial of antihypertensive treatment, for example, pill counts showed 68% adherence, while micro-electronic monitoring showed adherence of only 47% (Lee, Kusek et al. 1996).

C. Additional Outcomes
Additional assessment items will be administered at baseline only for diagnosis, characterizing participants and exploratory analysis. These include:

C.1. MDD Diagnosis
As recommended for clinical practice in VA settings by the 2009 VA/DOD Clinical Practice Guideline for Management of Major Depressive Disorder (MDD), the diagnosis of MDD will be obtained by diagnostic clinical interview supplemented by the self administered Patient Health Questionnaire (PHQ-9). The nine-item Patient Health Questionnaire (PHQ-9) is a validated self- or interviewer administered instrument that assesses DSM-IV-TR criterion symptoms and effects on functioning. In addition, it can be scored as a continuous measure to assess severity and monitor treatment response. The PHQ-9 can be administered in less than 2 minutes, and is
simple to score (Kroenke, Spitzer et al. 2001). PHQ-9 scores have been validated against DSM-IIIR, DSM-IV-TR, and functional status measures. Validity has been assessed against an independent structured mental health professional interview. PHQ-9 score $\geq 10$ had a sensitivity of 88% and a specificity of 88% for MDD (Kroenke, Spitzer et al. 2001; Dietrich, Oxman et al. 2003; Lowe, Grafe et al. 2004). In this study, the PHQ-9 also will help guide treatment decisions (Thase 2009).

C.2. Depression, Psychosis, Bipolar Disorder, Eating Disorders, PTSD, and Substance use Disorders

The MINI International Neuropsychiatric Interview (M.I.N.I.) is an easy to use psychiatric diagnostic interview that will be administered by the Study Coordinator or Independent Evaluator at baseline. The M.I.N.I. includes items that assess the hallmark symptoms of depression, psychotic disorders, bipolar disorder, PTSD, eating disorders and substance dependence. Information obtained from this interview will contribute to Study LSIs’ evaluation of participant eligibility with respect to exclusionary psychiatric diagnoses and to characterize the study population. The M.I.N.I. will not be used to diagnose MDD for entrance into the study, as clinical diagnosis supplemented with the PHQ-9 is more pertinent to the VA Healthcare System and to the goals of this study.

C.3. General Medical Well Being

The Cumulative Illness Rating Scale (CIRS) (Linn, Linn et al. 1968; Miller, Paradis et al. 1992) will be used to assess general medical conditions at baseline.

C.4. Early Life Adversity

Growing evidence suggests that early adversity may be a marker for distinct pathways to depression and may markedly impacts response to pharmacotherapy (Klein, Arnow et al. 2009). To assess physical and sexual abuse and abandonment we will administer the short form of the Adverse Childhood Experiences survey at baseline (ACE) (Bernstein, Stein et al. 2003).

C.5. Complicated Grief Screen

A brief (1-3 minutes) 12-item self-rated Complicated Grief Screen will be administered at baseline to record information on the prevalence of this condition in study participants and assess the association of complicated grief on the severity of depression and treatment response.
V. SUMMARY OF STUDY DESIGN AND METHODS

A. Background and Significance
The overall aim of VAST-D is to enhance treatment outcomes for representative outpatients diagnosed with nonpsychotic MDD and treated in primary or psychiatric VA care settings. Current evidence indicates that remission, the goal of treatment, is achieved in only about one-third of representative depressed outpatients treated for up to 14 weeks with an initial SSRI. Even with less ambitious outcomes, such as response (i.e., ≥50% improvement in symptoms), only about half of depressed outpatients reach that goal. In addition, even for those who do respond or remit, over one-third relapse in the subsequent 12 months. Thus, “next-step” treatments are often needed in clinical practice.

While ample double-blind controlled, randomized trials demonstrate all approved antidepressants are more effective than placebo and about equally effective to each other as first-step treatments, far less is known about relative strengths and liabilities of second- or third-step treatments such as strategies of switching or augmenting therapy and what are the most effective medications to use when augmenting. There is little empirical evidence to help clinicians make these important decisions.

This paucity of evidence-based data to guide “next-step” choices limits clinician’s ability to select the most effective, safest and least costly of the available choices. For this reason, finding an effective antidepressant treatment regimen remains a challenge for many patients and physicians. Clinicians are left relying on best guesses or expert testimony rather than firm, data-driven evidence. Thus, studies are badly needed to help identify benefits and risks of commonly used treatment strategies for the considerable number of depressed patients who fail an initial antidepressant trial.

VAST-D will provide answers to the two important questions for patients who have failed to achieve a satisfactory outcome to an antidepressant: 1) Is switching to another antidepressant as effective and better tolerated than augmenting with another antidepressant or a SGA? 2) Is augmenting with an atypical antipsychotic as effective and safe as augmenting with a widely used antidepressant? **VAST-D is powered to determine which of three commonly used**
“next-step” treatments maximally enhance remission rates, are most tolerable, result in lower attrition, provide sustained benefits and safety in the longer term and are most cost effective. VAST-D compares two different medication combinations, each against a monotherapy, and each other, as second-step medication treatments. The proposed study compares switching from an insufficiently effective selective serotonin or serotonin and norepinephrine reuptake inhibitor (SSRI or SNRI) or mirtazapine with a frequently used next-step antidepressant that has a different mechanism of action, the norepinephrine and dopamine reuptake inhibitor, bupropion-SR (BUP-SR); vs. adding bupropion-SR to the SSRI,SNRI or mirtazapine creating the very broad spectrum combination (antidep + BUP-SR); vs. adding an atypical antipsychotic agent, aripiprazole, that acts by a wider range of different mechanisms (beyond reuptake inhibition) (antidep + ARI). The rationale for selecting these three “next-step” treatments is described in greater detail in Section XIV.

B. Study Population
VAST-D will randomize 1518 total participants (target of 51 participants at each of 30-35 participating sites) of both genders and all ethnic/racial and socioeconomic backgrounds. All patients will meet DSM-IV TR criteria for nonpsychotic MDD. The diagnostic criteria for eligibility will be established clinically, and with the 9-item Patient Health Questionnaire (PHQ-9). Only participants with a suboptimal outcome on well documented, adequately delivered (dose and duration) treatment with a SSRI, SNRI or mirtazapine will be eligible for the study. Failure to achieve an adequate outcome will be ascertained by a QIDS-C-16 \( \geq 16 \) (considered severe depression) after at least 6 weeks of treatment or \( \geq 11 \) (considered moderately severe depression) after at least 8 weeks. Otherwise, the inclusion criteria are broad and the exclusion criteria are few; participants with most comorbid general medical or psychiatric disorders are generally included to provide a broadly representative sample. Suicide risk will NOT be considered an exclusion unless in-patient care is required to reduce risk to an acceptable level. VAST-D will implement an aggressive suicide risk management strategy modeled on the approach pioneered in STAR*D. The complete inclusion and exclusion criteria, and rationale for key decisions, are described in Section VII: A-C. Final determination for eligibility will be made by the study clinician.
C. Treatment Regimens

C.1. Prior to Consent and Randomization

To optimize generalizability and external validity of findings, participants may enter the study on any SSRI, SNRI or mirtazapine that their treating clinician has prescribed as long as they are not taking bupropion, aripiprazole or other SGAs. By closely simulating routine outpatient practice and allowing the clinician to select the antidepressant, treatments may be maximally tailored to individual participants with general medical, ethnic, and psychiatric diversity.

To ensure that the participants are truly in need of a “next-step” treatment, they must have been on the antidepressant for at least 6 weeks (if still severely depressed) or 8 weeks (if still moderately depressed), with at least the most recent 3 of those weeks at a stable “optimal” dose (as described in Section VII.D). To ensure that participants are not pushed to the next step too quickly, clinicians will be advised to treat patients beyond these minimal durations if they feel more time on drug or higher doses are warranted. They will be encouraged to refer patients to the study only when they feel a “next-step”, beyond a dose increase, is indicated.

C.2. Randomized Treatment

Randomized treatment includes both an acute treatment phase and a longer term continuation treatment phase.

C.2.1. Acute Treatment Phase

The primary goal of this study is to compare the three medication treatments in terms of remission rates (QIDS-C16) during up to 12 weeks of treatment. Patients will be randomized (1:1:1 ratio) to bupropion-SR alone (BUP-SR) (n=506), antidepressant plus bupropion-SR (antidep + BUP-SR) (n=506), or antidepressant plus aripiprazole (antidep + ARI) (n=506). Treatment will be guided by clinician-rated symptom measures (the PHQ-9) and global side effects measures (the Frequency, Intensity, and Burden of Side Effects Rating or FIBSER) obtained at each treatment visit. Treatment visits will occur at baseline and at weeks 1, 2, 4, 6, 8, 10, and 12 to ensure delivery of appropriate and yet vigorous and tolerable pharmacotherapy.
C.2.2. Continuation Treatment Phase

Because depression is a chronic and recurrent illness, it is important to look beyond the first several weeks of treatment to determine the effectiveness of any treatment. One of the unique aspects of this study is that it provides important data on the longer term effectiveness, safety, tolerability and costs of the acute treatments. Thus, participants who tolerate the acute treatment and achieve “adequate benefit” at 12 weeks will enter the 24 week Continuation Treatment, during which the initial treatment will continue and visits will occur at monthly intervals. Adequate benefit will be defined as a QIDS-C\textsubscript{16} \leq 10 (all participants with a QIDS-C\textsubscript{16} \leq 5 and those with a QIDS-C\textsubscript{16} of 6 - 10 if they and their clinicians are satisfied with their progress and prefer to remain on the medication or combination longer). Other participants will exit the study and be treated as clinically indicated. The doses used during the Continuation Phase may be adjusted if participants and clinicians raise (or lower) doses due to an exacerbation of symptoms or the development/persistence of unacceptable side effects.

D. Outcome Measures

VAST-D is designed to compare the three “next-step” treatments described above using broad and multidimensional outcomes: symptomatic remission, response and relapse rates, anxiety, suicidal ideation and behaviors, function and quality of life, adherence, tolerability, side effects, safety, health care costs, and satisfaction with treatment. The primary outcome measure for the VAST-D study will be remission as defined by a QIDS-C\textsubscript{16} \leq 5 for 2 consecutive visits during the 12 weeks of acute, randomized intervention. Key secondary outcomes will be response (\geq 50\% improvement from baseline on the QIDS-C\textsubscript{16} and as a separate response measure, a score of 1 or 2 on the Clinical Global Improvement Scale) at the end of acute and continuation treatment, percentage change in the QIDS-C\textsubscript{16} from baseline to end of acute and continuation treatment, and relapse (QIDS-C\textsubscript{16} \geq 11) after remission or during continuation treatment. The QIDS-C\textsubscript{16} will be administered at each visit. In addition, several measures of side effect burden, safety, quality of life and functioning, and health related costs will be administered at regular intervals. A more complete description of all outcome measures and a discussion of the rationale for their selection are found in Section IV.
E. Sample Size
The target sample size for VAST-D is 1518 randomized participants (506 per treatment group) enrolled over 29 months from 30-35 primary care and psychiatric care sites. This sample size will provide 90% power to detect a 10% difference in remission between augmentation treatments and switch to bupropion-SR monotherapy in the acute treatment phase, and will provide ample power to identify clinically meaningful differences between treatments in longer term safety and health related costs. More detail on Power estimates for primary, secondary and tertiary hypotheses are provided in Section XXIII: B and C.

F. Study Monitoring
The study will be monitored externally by an independent Data Monitoring Committee (DMC) composed of outside experts in depression, clinical trials, bioethics and biostatistics. The accumulating data will be presented to the DMC, who will be charged with the decision of whether or not to recommend stopping the trial early for safety, futility, or treatment efficacy. One interim analysis of the primary endpoint at 12 months (prior to ending enrollment into the trial) is proposed for the purpose of sample size re-estimation. Depending on the outcome, the interim analysis may be used to recommend the trial be stopped early for efficacy or futility. Throughout the recruitment and follow-up phase of the trial, the Executive Committee and Coordinating Center will continually monitor sites for patient intake, protocol adherence, data quality, and completeness of follow-up. Participating sites will be closely monitored for recruitment, particularly early in the enrollment phase of the study, and will not be continued in the study if they fail to achieve and acceptable recruitment rate. Details of the study monitoring activities are described in Section XX.
**Inclusion Criteria**

1. DSM-IV diagnosis of single or recurrent, non-psychotic, major depressive disorder
2. Currently taking a selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI) or mirtazapine for major depressive disorder
3. Need for “next-step” treatment based on documented suboptimal outcome from current antidepressant treatment for major depressive episode
   - QIDS-C ≥16 after at least 6 weeks treatment or QIDS-C ≥11 after at least 8 weeks
   - At least 3 weeks at a stable “optimal” dose
4. Age ≥18 years of age

**Exclusion Criteria**

1. Prior inadequate response after an adequate treatment trial or clear cut intolerance to either of the study medications (aripiprazole or bupropion).
2. Current treatment with bupropion, aripiprazole or any antipsychotic agent.
3. Lifetime history of bipolar disorder, schizophrenia, schizoaffective disorder, or psychosis not otherwise specified.
5. Current diagnosis of an eating disorder or a seizure disorder.
6. High suicide risk currently requiring acute intervention (other than outpatient of depression treatment).
7. Unstable, serious medical condition or one requiring acute medical treatment, or anticipation of hospitalization for extended care.
8. Requiring immediate hospitalization for psychiatric disorders.
9. Physiologic substance dependence requiring detoxification (excluding nicotine) in the past 30 days (substance abuse is not an exclusion criteria).
10. Taking any concomitant medications that contraindicate treatment options or augmenting agents known to have an antidepressant effect.
11. Concurrent or recent participation (within the last 30 days) in another conflicting clinical trial with a mental health, investigational drug, or medical device intervention
12. Female - pregnant or lactating or planning to become pregnant.
13. Patient was not able or willing to provide informed consent. or changed mind about participating.
14. Patient was not referred to the study.

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**BASELINE**

Diagnosis, depression history, and assessment
If QIDS-C ≥11, enter randomized treatment phase

**RANDOMIZATION** – 1:1:1

**Acute Treatment** (12 Weeks)

- **Bupropion-SR Switch**
  - (n=506)
  - Follow 12 weeks for remission, response, relapse and safety

- **Bupropion-SR Augmentation**
  - (n=506)
  - Follow 12 weeks for remission, response, relapse and safety

- **Aripiprazole Augmentation**
  - (n=506)
  - Follow 12 weeks for remission, response, relapse and safety

**Continuation of Treatment if QIDS-C ≤ 8 (possibly if QIDS 9-10)**

- **Bupropion-SR Switch**
  - Follow: Up to 24 additional weeks for sustained remission and response, relapse, and safety

- **Bupropion-SR Augmentation**
  - Follow: Up to 24 additional weeks for sustained remission and response, relapse, and safety

- **Aripiprazole Augmentation**
  - Follow: Up to 24 additional weeks for sustained remission and response, relapse, and safety

**36 Weeks:** Closeout and Return to Standard Clinical Care
VI. RATIONALE FOR OVERALL DESIGN CONSIDERATIONS

Many of the key decisions regarding methodology were made in the interests of maintaining scientific rigor while balancing internal and external validity. Thus, the overall design is a hybrid intervention study, combining aspects of both efficacy and effectiveness paradigms (Wells, Miranda et al. 2004), ideally suited to translate research (bench) into practice (bedside) (Schneider, Tariot et al. 2001; Sachs, Thase et al. 2003; Rush, Fava et al. 2004).

The goal of an efficacy trial is to determine what works under ideal circumstances, maximizing internal validity by controlling all extrinsic factors that can contribute variability to treatment effects. The randomized, placebo-controlled clinical trial is the gold standard. Essential features are the high degree to which participant selection is narrow and homogenizing, carrying out interventions with highly trained clinicians following formalized protocols, masking clinicians and participants from the treatment assignment, and focusing on symptoms as the primary outcome. The advantage of an efficacy study is that it definitely answers the question of whether a medication works better than placebo or another medication under ideal circumstances. The disadvantage is that results may not apply to “real” patients in real life circumstances, delivered by “real” doctors in practice (Depp and Lebowitz 2007).

In contrast, the goal of an effectiveness trial is to maximize generalizability and to “address practical questions about the risks, benefits, and costs of an intervention as they would occur in routine clinical practice” (Tunis, Stryer et al. 2003). The selection of participants is broad with few exclusions, a wide-array of outcomes is utilized, interventions are delivered in actual practice settings in a non-rigid fashion, dosing is flexible and patients and clinicians are not masked to treatment. In this way, external validity is emphasized.

The proposed study is a hybrid, containing elements of an efficacy study (e.g. random assignment to treatment conditions, use of objective outcome measures, masked rater for primary outcome, independence of outcome assessment from treatment delivery, monitoring of treatment delivery and compliance monitoring) and of an effectiveness trial (e.g. broad inclusion and minimal exclusions, clinical guidelines mixed with clinical judgment for dosing and duration of treatment, comparison treatments all equally likely of being effective and safe, treatment
provided in actual clinics by practicing clinicians, evaluation of cost effectiveness and other outcomes beyond disease symptoms, provider and patient not blind to treatment assignment, and relatively long-term follow-up). Most of these design decisions are in the service of maximizing the probability that findings will be applicable to typical VA patients with nonpsychotic major depression and readily transportable to all VA primary care and psychiatry specialty clinics and patients.

The rationale for specific methodological decisions is imbedded in the corresponding sections throughout the protocol.

VII. PATIENT POPULATION

A. Inclusion Criteria
   1. DSM-IV diagnosis of single or recurrent, non-psychotic, major depressive disorder
   2. Currently taking a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI) or mirtazapine for major depressive disorder
   3. Need for “next-step” treatment based on documented suboptimal outcome from current antidepressant treatment for major depressive episode
      - at least 6 weeks treatment with a QIDS-C16 ≥ 16
      or
      at least 8 weeks with a QIDS-C16 ≥ 11
      and
      - at least 3 weeks at a stable “optimal” dose
       (see Section VII.D and Table 2 for “optimal” dose guidelines)
   4. Age: 18 years of age or older

B. Exclusion Criteria
   1. Prior inadequate response after an adequate treatment trial or clear cut intolerance to either of the study medications (aripiprazole or bupropion) (Determination should be based on documented evidence; See Section VII.C for definitions)
   2. Current treatment with bupropion, aripiprazole or any other antipsychotic agent (See Section XIV.D for washout guidelines and approved alternatives to antipsychotics)
3. Lifetime history of bipolar disorder, schizophrenia, schizoaffective disorder, or psychosis not otherwise specified
4. Current diagnosis of Dementia
5. Current diagnosis of an eating disorder or a seizure disorder
6. High suicide risk currently requiring acute intervention (other than outpatient treatment of depression)
7. Unstable, serious medical condition or one requiring acute medical treatment, or anticipation of hospitalization for extended care
8. Requiring immediate hospitalization for psychiatric disorders
9. Physiologic substance dependence requiring detoxification (excluding nicotine) in the past 30 days (substance abuse is not an exclusion criteria)
10. Taking any concomitant medication that contraindicates treatment options or augmenting agents known to have an antidepressant effect (see Section XIV. D for examples and exceptions)
11. Concurrent or recent participation (within the last 30 days) in another conflicting clinical trial with a mental health, investigational drug, or medical device intervention (Non-investigational studies and non-conflicting strategy trials are not an exclusion; Participation in other clinical trials will be evaluated for approval by the Executive Committee according to this criteria on a case by case basis and these determinations will be documented)
12. Female - pregnant or lactating or planning to become pregnant
13. Patient was not able or willing to provide informed consent; or changed mind about participating prior to randomization
14. Patient was not referred to the study

C. Rationale for Participant Selection
The rationale for selecting individuals with MDD who experience suboptimal outcomes to standard antidepressant treatment is covered in detail in Section I. The rational for requiring a QIDS-C16 ≥ 11 at week 8 is that the vast majority of individuals who are going to remit or respond by the end of the acute treatment phase would be expected to be considerably less severely symptomatic by then (a QIDS-C16 ≥ 11 is equivalent to a Hamilton Depression Scale Score of ≥ 14, indicating “moderately severe” depression) (Rush, Warden et al. 2009). If the
individual already has had his or her dose maximized for 3 or more weeks, all treatment
guidelines suggest it is time to switch medications or augment with another agent (Tunis, Stryer
et al. 2003). We considered enrolling participants with even lower QIDS-C_{16} scores, as they,
too, may require next step treatments, but we were concerned that it would be difficult to
demonstrate treatment differences with too low baseline ceilings, and also felt uneasy about
augmenting with antipsychotics for up to 36 weeks for individuals whose depression severity
was not at least moderately severe.

On the other side of the severity spectrum, however, most clinician-patient dyads would not wait
8 weeks to alter medication strategies for very severe depressive symptoms. Therefore, we
elected to also allow participants with a QIDS-C_{16} \geq 16 (severe depression, equivalent to a
Hamilton Depression Scale score of \geq 20), to enter the study after 6 weeks. Most patients who
are that depressed after 6 weeks of treatment at optimal doses would not wait 2 more weeks to
“do something”. Indeed, the 2009 VA/DoD MDD Depression Treatment Guidelines
recommends taking action after 6 weeks if a patient has not achieved \geq 25\% symptomatic
improvement, citing evidence that such patient are not likely to improve if left alone (Quitkin,
McGrath et al. 1996). Rather than expose these patients to undue pain and suffering and risk of
suicide, and/or lose them to “open” treatment in the clinic, we will allow them to enroll in the
study.

In general, the inclusion/exclusion criteria are broad so as to acquire a sample representative of
persons with MDD who would receive “next-step” medication in everyday practice. However,
persons with medical contraindications that preclude randomization to any study treatment (such
as those with anorexia nervosa, bulimia or seizure disorders for bupropion, or older persons with
dementia) are excluded. In addition, participants with schizophrenia, schizoaffective disorder or
bipolar disorder are excluded because they have a primary psychiatric condition that requires a
different initial treatment. Participants with currently active and clinically significant substance
abuse are eligible (so long as inpatient care is not required clinically at study entry), though
participation in a substance abuse program will be encouraged by their clinician. Participants
with active substance dependence who require detoxification are not eligible for reasons of
medical safety. Finally, patients with suicidal ideation will be eligible as long as they do not
require immediate inpatient care. There is no reason to think there is a better available treatment for depressed participants with suicidal ideation than the ones in this study. Indeed, protocol participation is not a greater risk for these participants than usual care. Participants who become so suicidal that inpatient care is needed will be removed from the study and provided appropriate treatment.

Potential participants with documented evidence of prior inadequate response after an adequate treatment trial or clear cut intolerance to either of the study medications (aripiprazole or bupropion) will be excluded from the study. It would not be in the best interest of the patient or the study to rechallenge medications known to have resulted in a treatment failure for such patients. An inadequate response is defined as a lack of clinically significant improvement in symptoms noted by a treating clinician after a trial of at least 6 – 8 weeks, with at least 3 of those weeks at a dosage of at least 300 mg daily of bupropion (or bupropion-SR or bupropion-XL) or at least 10 mg daily of aripiprazole. Participants will be considered intolerant to a study medication if they were unable to complete at least a three-week trial at the target dose (300 mg daily of bupropion or 10 mg daily of aripiprazole) due to adverse effects or complications, or if the dose for response was increased to greater than 300 mg for bupropion or 10 mg for aripiprazole and the participant can no longer tolerate this dose.

In the event that there is incomplete or inconsistent information on previous treatment trials of bupropion or aripiprazole (e.g., patient recall of non-VA care, patient known to be an inaccurate historian, medication prescribed for another indication or incomplete records), the LSI should review the information and make an 'informed' decision. This decision should be based on record review, discussion with treating clinician and an interview with patient. If the evidence suggests intolerance to either medication, the patient should be excluded. If the SI's best clinical judgment is that the patient has not shown clear cut intolerance to either drug, a note justifying the decision should be entered into the research records and CPRS.

D. Definition and Rationale for “Adequate Treatment Trial” of Index Antidepressant
The importance of defining an adequate treatment trial before randomizing individuals in this “next-step” trial is to ensure that participants are truly in need of switching or augmenting and
not merely inadequately treated in terms of dose or duration. We want to avoid randomizing participants who are on the brink of responding if simply provided watchful waiting or an increased dose of their medication. At the same time, we do not want participants to linger in a failed treatment for any longer than necessary. Unfortunately, the psychiatric literature is not fully consistent on what dose or duration of treatment constitutes an adequate trial. For our purposes, we will require documentation of remaining severely depressed (QIDS-C16 ≥16) for at least 6-weeks at a moderate to high dose of a SSRI, SNRI or mirtazapine or moderately depressed (QIDS-C16 ≥11) after at least 8 weeks of treatment, with at least the 3 most recent weeks at a stable “optimal” dose (according to dosing guidelines in Table 2).

Ideally, for the current (index) antidepressant trial to qualify for an adequate trial of a SSRI, SNRI or mirtazapine, the patient must have been prescribed at least the highest dose in the guidelines included in Table 2, “Guidelines for Adequate Antidepressant Dosing Prior to Randomization.” However, a potential participant may have reached the highest tolerated or recommended dose of their index antidepressant for his/her specific circumstances (age, comorbidities) and, given such circumstances, may still be an ideal candidate for augmentation or switching. The guidelines in Table 2 are intended to be representative of the patient population sought after in VAST-D, though it is recognized that such guidelines cannot be a complete substitute for clinical judgment and there will be patients who will not strictly meet these guidelines (for example, there may be uncertainty whether the duration or dosing guideline is sufficiently met in a patient ≥ 65 years of age). Therefore, LSIs will contact the Study Chairs for consultation on such patients and, should the decision be to declare the treatment trial adequate for entering the study, will clearly document the discussion and decision to randomize at a lower dose in the patient’s medical and research records.
Table 2. Guidelines for Adequate Antidepressant Dosing Prior to Randomization

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>citalopram</td>
<td>20 mg</td>
</tr>
<tr>
<td>desvenlafaxine</td>
<td>100mg</td>
</tr>
<tr>
<td>duloxetine</td>
<td>60 mg</td>
</tr>
<tr>
<td>escitalopram</td>
<td>20 mg</td>
</tr>
<tr>
<td>fluoxetine</td>
<td>40 mg</td>
</tr>
<tr>
<td>mirtazapine</td>
<td>30 mg</td>
</tr>
<tr>
<td>paroxetine</td>
<td>40 mg</td>
</tr>
<tr>
<td>paroxetine CR</td>
<td>50 mg</td>
</tr>
<tr>
<td>sertraline</td>
<td>150 mg</td>
</tr>
<tr>
<td>venlafaxine IR</td>
<td>225 mg</td>
</tr>
<tr>
<td>venlafaxine XR</td>
<td>225 mg</td>
</tr>
</tbody>
</table>

Adapted from Sovason and DeBattista, Antidepressant dosing for the acute treatment of unipolar depression. Primary Psychiatry, 2009, 16 (10): 30-36.

1 New antidepressants will be added as they come on the market and are adopted in the VA.

2 Lower doses may be allowed, with Study Co-Chair approval, if lower dose is highest tolerated or recommended dose.

We also considered whether to require a run-in treatment period to ensure that participants were indeed optimally treated and in need of a “next-step” treatment. Open-label or masked run-in phases are commonly used in antidepressant treatment trial protocols. There are two types: placebo (PBO) run-in and active treatment run-in. The purpose of PBO run-in is, purportedly, to eliminate PBO responders and to accentuate drug-PBO differences in the randomized phase.
PBO run-in fulfills neither purpose (see, for example, Trivedi and Rush (1994)), and have been subject to strong ethical critique as in Mann (2007).

The second type, active-treatment run–in, has been used less frequently, but has been proposed as a method to create a prospectively defined cohort with inadequate response to first-line treatment. A prime example is STAR*D, the NIMH supported trial in which 4,000 individuals were treated in order to randomize 2600 that had not achieved remission with the first treatment. Though time consuming, expensive, logistically challenging, and an approach that increased drop-out, the prospective run-in was determined to be useful in order to eliminate patients that had not received adequate treatment (i.e. the appropriate dose of the appropriate treatment for a sufficient duration). Alternatives to this were considered in STAR*D but were rejected because they depended on unreliable patient recall and inadequate medical chart records from multiple providers.

We have revisited these considerations in the design of VAST-D and have determined that the unified, integrated electronic medical record of the VA Healthcare System would support a more efficient approach. Briefly, after a patient is referred to VAST-D by the clinician treating the patient for depression, pre-screened for a current episode of MDD and consented, further screening of these individuals will include a diagnostic clinical interview (~30 minutes) by the Study Coordinator, supplemented by the PHQ-9, to determine their true eligibility for study treatment. The diagnostic clinical interview will assess DSM-IV-TR criteria for current and past MDD, current and past treatment and current treatment response. Next, information will be supplemented by data extracted from the medical record that corresponds to the often-used Antidepressant Treatment History Form (ATHF) of Sackeim (Sackeim 2001). Discrepancies between the data obtained from the clinical interview and the record review will be discussed with the Site Investigator (SI) and treating clinician, and resolved, before the patient is randomized. With this approach, a history of psychiatric diagnoses and antidepressant medication doses and durations of prescribed treatments will be available to the study team and an expensive and resource dense run-in period will not necessary to achieve our scientific aims.
The patient’s primary physician (treating clinician) is involved in the referral process but will not be completing assessments for eligibility. The PHQ-9, the clinical interview and any other screening assessments will be administered by the SI or study personnel and completed by the patient after the patient has signed the Informed Consent.

VIII. PATIENT RECRUITMENT AND SCREENING

Recruitment: The Investigator and the Study Coordinator (full-time) will work closely with staff in the psychiatric programs and primary care at each VA Medical Center. In-service seminars will be held to explain the purpose of the study and eligibility criteria to hospital staff at the beginning of the study and periodically throughout the recruiting period. Primary care clinics evaluate patients for depression at regular clinic visits, and patients with a diagnosis of depression may be referred to the study for screening. Potential participants initially will be screened for the diagnosis of MDD using the site’s standard procedure. All study personnel and investigators, however, will use standard inclusion/exclusion criteria for determining study eligibility. Screening may include review of potential participant responses to the PHQ-9 as recommended by the 2009 VA/DoD Clinical Practice Guideline for Management of Major Depressive Disorder or other measures if already in place locally. However, neither the PHQ-9 nor any other diagnostic instruments, including the clinical interview, will be administered for the purposes of this study until after informed consent is obtained. No participant will be excluded on the basis of race or ethnicity.

Screening Process: Outpatients with a clinical diagnosis of major depressive disorder up to the time that the full target sample has been recruited will be identified for screening for eligibility. Before a patient is contacted, the patient’s primary clinician will be asked to: a) confirm the diagnosis; b) review current medications; c) invite the patient to meet with the research team to learn about the study and be screened for eligibility. If the patient is not eligible, the reason will be documented in progress notes and on the Screening Form. No assessments will be administered for research purposes, including screening, until the patient has signed the informed consent.
Patients who agree to participate in further screening will be asked if they would be willing to be randomized to either switching their current antidepressant to another antidepressant, adding an additional antidepressant to their current medication or adding an antipsychotic medication. If interested, additional information about the study will be given to the patient and procedures for administering informed consent will be followed (see Section IX.A for Informed Consent Procedures).

Table 3. Screening and Eligibility Assessments

<table>
<thead>
<tr>
<th>Domain</th>
<th>Measure</th>
<th>Time (Minutes)</th>
<th>How</th>
<th>Who</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intake</td>
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<tr>
<td>Consent</td>
<td>Consent</td>
<td>20</td>
<td>Interview</td>
<td>SC / IE</td>
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<tr>
<td>Characteristics</td>
<td>ATHF</td>
<td>EF</td>
<td>15</td>
<td>Interview</td>
</tr>
<tr>
<td></td>
<td>(Inclusion/Exclusion)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
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<td>30-40</td>
<td>Interview</td>
<td>SC/ IE</td>
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<tr>
<td></td>
<td>PHQ-9</td>
<td></td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td></td>
<td>M.I.N.I.</td>
<td></td>
<td>Interview</td>
<td>SC/ IE</td>
</tr>
<tr>
<td>Symptoms</td>
<td>QIDS-C_{16}</td>
<td>6</td>
<td>Interview</td>
<td>IE /SC</td>
</tr>
<tr>
<td>GMCs</td>
<td>CIRS</td>
<td>5</td>
<td>Interview</td>
<td>IE /SC</td>
</tr>
<tr>
<td>Total Time</td>
<td></td>
<td>75-90</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ATHF = Antidepressant Treatment History Form  
CIRS = Cumulative Illness Rating Scale  
EF = Screening Form  
GMC = Good Medical Care  
PHQ-9 = Patient Health Questionnaire  
QIDS-C_{16} = 16-item Quick Inventory of Depressive Symptomatology - Clinician-report  
M.I.N.I. = M.I.N.I. International Neuropsychiatric Interview (depression, bipolar, substance use, eating disorder, PTSD, and psychosis modules only)  
SC = Study Coordinator  
IE = Independent Evaluator

As recommended in the *VA/DoD Clinical Practice Guideline for Management of Major Depressive Disorder*, DSM-IV-TR criteria will be administered to confirm the diagnosis of MDD and obtain necessary information about symptoms, symptom severity, and effects on daily functioning. As described above, the electronic medical record will be a useful source to further document past treatments and their outcomes. All reasons for ineligibility or refusal of study participation will be documented. Advantages of this comprehensive screening is that it provides data on the representativeness of the final sample, reasons for not participating in the study, and the acceptability of the use of antipsychotic medication in this population.
The patient’s primary physician (treating clinician) is involved in the referral process and will not be completing assessments for eligibility. The PHQ-9 and any other screening assessments will be administered by the SI or study personnel and completed by the patient after the patient has signed the Informed Consent.

IX. HUMAN RIGHTS ISSUES AND INFORMED CONSENT

A. Consent Procedure

After a patient has been identified by clinical record review and referred to the study team by the patient’s treating clinician, a member of the study team will initiate the informed consent process with the patient. The study will be introduced and explained to the patient and the patient will be presented with the detailed informed consent form. Subsequently, prior to randomization, the site investigator (or a designated study physician) will review and discuss the study with the patient and answer any questions that the patient might have. The general purpose of the study will be delineated. The treatment comparisons will be clearly described. The randomization process, along with the concept of blinded ratings and the timeline, including what is expected of the patient will also be described. The risks associated with treatments and procedures will also be addressed. The importance of patient privacy will be stressed describing the process for maintaining this confidentiality. Discussions about the study and the patient’s eligibility for the study will occur in a private setting. Patients will be given the opportunity to take a copy of the informed consent document home with them to review by themselves or with family members.

Patients who are potentially eligible for the study and interested in participating will be asked to sign the informed consent. It must be ensured that the patient understands every aspect of the trial, including its risks and benefits, prior to signing the informed consent.

If the patient agrees to participate, his/her consent to participate in the study will be recorded on the Agreement to Participate in Research form (VA form 10-1086, See Appendix A – Human Rights Considerations). The original will be placed in the patient’s research record. Copies of the signed consent form will be provided to the patient, the Research Office at the participating
site (if required by the IRB), and must also be faxed (or mailed by tracked mail) to West Haven CSPCC at the time of enrollment in the study.

Informed consent requires that the patient understand the details of the study and agrees, without coercion, to participation in the study. To obtain informed consent, the following information shall be provided to each subject:

- Name of the study
- Names of the Site Investigators
- Explanation that the study involves research
- Explanation of the purpose of the study
- Explanation of the treatment procedures
- Description of randomization.
- Description of the risks and benefits of participation in the study
- A description of alternatives to participation in the study
- Explanation that all records will be kept confidential, but that records may be examined by representatives of the VA and/or the FDA
- Who to contact for questions about the research and about subjects’ rights
- Who to contact in the event of research-related injury
- A statement that participation in the study is voluntary and that a decision not to participate or to withdraw from the study after initially agreeing involves no penalty, loss of benefits or reduction in access to medical care
- A statement that treatments provided as part of this study are free.

Merely obtaining signature consent from the patient does not constitute informed consent. However, the use of a standardized consent form aids in assuring that subjects receive adequate and consistent information about the trial and have consented to participate. In conjunction with the informed consent procedure patients will review and be asked to sign the Authorization for Release of Protected Health Information From as required by HIPAA.

**B. Surrogate Consent**

No surrogate/proxy consent will be allowed. For patients who are competent to give informed consent and judged not able to carefully read the consent form because of either literacy issues or impaired vision, the informed consent will be read to the patient and his/her written consent will be obtained if he/she is willing to participate.
C. Risks and Benefits
All patients participating in this study receive treatment for depression as determined by their treating physician prior to study enrollment. Major risks attributable to study drugs will be described in the informed consent document.

D. Informed Consent
A copy of the signed informed consent form and a copy of the signed privacy authorization form will be sent to CSPCC by secure facsimile or tracked mail. After obtaining informed consent, but before randomization, patients will complete additional screening assessments to determine final eligibility. After obtaining informed consent, patients will be classified as enrolled in the study and be followed for safety until they are excluded from the study at which point they will be referred back to their referring clinicians for treatment. For patients who are eligible, all other baseline assessments will be completed prior to randomization. Since most of the screening process cannot be initiated until the potential participant gives informed consent, it is possible that many consented participants will be found to be not eligible for the study after the completion of all screening assessments, or the potential participant may change his/her mind about participating and is not randomized. In this study, it will not be unreasonable or unexpected for a study site to consent twice the number of participants than those who are randomized, for a total of about 3000 participants enrolled study-wide.

If new information becomes available during the course of a study regarding a significant risk that could affect a participant’s willingness to enter or continue to participate in a study, Study Investigators will be notified of the new information by the Central Research Pharmacy and CSPCC, and the Site Investigator will notify the participant. If the information is associated with more than a minimal risk to the participant, the informed consent document may need to be changed (per CSP policy) and participants who have already been enrolled in the study may need to be re-consented.

E. Certificate of Confidentiality
A Certificate of Confidentiality has been obtained from the Federal Government through the National Institute of Mental Health. This helps protect participant privacy by allowing investigators to refuse to release personal and other research information outside of the research study, even by a court order. By law, information can still be released in cases of suspect child
abuse, elder abuse, an intent to harm oneself or others, or if the participant has an infectious disease for which State or Federal law requires reporting. The Certificate of Confidentiality does not prevent the participant or a participant’s family from releasing data about the participant or his/her involvement in this study.

X. BASELINE ASSESSMENT

When feasible, the screening for eligibility, consenting process and baseline data collection will be completed on the same day. However, in order to provide potential participants with time to consider enrollment, minimize participant burden and fatigue, and to provide time to complete all screening and baseline assessments it is more likely that baseline assessment will require more than one day to be completed. A common practice may be to conduct a consent/screening visit (see Table 3) and a separate baseline visit (see Table 4). No time limit will be stipulated between the screening and baseline visits; however, a thorough review of the participant’s CPRS record is required prior to randomization to ensure the participant’s eligibility status has not changed since the screening visit. Baseline assessments can be divided into 2 or more sessions, but the baseline assessments must be completed within one week prior to randomization. If not, then the baseline assessments will need to be updated or repeated. Time-sensitive assessments such as the QIDS-C16, PHQ-9, Columbia Suicide Severity Rating Scale (as needed), vital signs and side effect checklist must be completed on the day of randomization.

Approximately 1 tablespoon of blood will be drawn for local laboratory test to establish a baseline for safety monitoring of possible side effects of study medications, in particular, problems with kidney or liver function. The results of the baseline tests will also alert the study investigator to any pre-existing problems or medical conditions that might preclude randomization. For women of child-bearing age, a urine sample (less than one ounce) will be collected for a pregnancy test to be performed prior to randomization to be sure the participant is not pregnant prior to the initiation of study medications.

Screening forms will be completed for all enrolled (consented) patients. Screening Assessments are tabulated in Section VIII. Baseline assessments will be completed for enrolled patients who are determined to be eligible for the study and are scheduled for randomization. Table 4 summarizes Baseline Assessments.
<table>
<thead>
<tr>
<th>Domain</th>
<th>Measure</th>
<th>Time (Minutes)</th>
<th>How</th>
<th>Who</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>BCDF</td>
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<td>Interview</td>
<td>Study Coordinator</td>
</tr>
<tr>
<td><strong>Depressive Symptoms</strong></td>
<td>QIDS-C16*</td>
<td>6</td>
<td>Interview</td>
<td>Independent Evaluator</td>
</tr>
<tr>
<td></td>
<td>CGI-S</td>
<td>1</td>
<td>Interview</td>
<td>Independent Evaluator</td>
</tr>
<tr>
<td></td>
<td>PHQ-9</td>
<td>3</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td>Associated Symptoms</td>
<td>BAI</td>
<td>5</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td></td>
<td>C-SSRS</td>
<td>10</td>
<td>Interview</td>
<td>Study Coordinator/IE</td>
</tr>
<tr>
<td></td>
<td>PCL-5</td>
<td>5</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td></td>
<td>Mania/Hypomania</td>
<td>5</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td></td>
<td>Positive Health</td>
<td>3</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td>Childhood Adversity</td>
<td>ACE</td>
<td>5</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td>Complicated Grief</td>
<td>Grief Screen</td>
<td>5</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td>Side Effects</td>
<td>Lab Studies</td>
<td>10</td>
<td>Blood draw</td>
<td>Study Coordinator</td>
</tr>
<tr>
<td></td>
<td>SE Checklist</td>
<td>5</td>
<td>Interview</td>
<td>Study Coordinator</td>
</tr>
<tr>
<td></td>
<td>Vital Signs</td>
<td>4</td>
<td>Exam</td>
<td>Study Coordinator</td>
</tr>
<tr>
<td></td>
<td>BAS</td>
<td>4</td>
<td>Interview</td>
<td>Study Coordinator</td>
</tr>
<tr>
<td></td>
<td>ASES</td>
<td>3</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td></td>
<td>FIBSER</td>
<td>2</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td></td>
<td>SAE / AE</td>
<td>10</td>
<td>Interview</td>
<td>Study Coordinator</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>Q-LES-Q</td>
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<td>Participant</td>
</tr>
<tr>
<td></td>
<td>EQ-5D</td>
<td>3</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td></td>
<td>WSAS</td>
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<td>Participant</td>
</tr>
<tr>
<td></td>
<td>WPAI</td>
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<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td>Health Related Costs</td>
<td>Income and Employment</td>
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<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td></td>
<td>Use of Non-VA Resources</td>
<td>2</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td>Medications</td>
<td>Rx</td>
<td>2</td>
<td>Interview</td>
<td>Study Coordinator</td>
</tr>
<tr>
<td></td>
<td>CMT</td>
<td>2</td>
<td>Interview</td>
<td>Study Coordinator</td>
</tr>
<tr>
<td><strong>Total Time</strong></td>
<td></td>
<td>65-75</td>
<td></td>
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</table>

ACE = Adverse Childhood Experiences
ASES = Arizona Sexual Experience Scale
BAI = Beck Anxiety Inventory
PCL-5 = PTSD Checklist for DSM-5 (if MINI = PTSD)
BAS = Barnes Akathisia Scale
BCDF = Baseline Clinical and Demographic Form
CGI-S = Clinical Global Impression- Severity
CMT = Concomitant Medication Tracking form
C-SSR = Columbia Suicide Severity Rating Scale
EQ-5D = EuroQoL Health Questionnaire
PHQ-9 = Patient Health Questionnaire
QIDS-C16 = 16-item Quick Inventory of Depressive Symptomatology - Clinician-report (* if not the same day as first screening.)

FIBSER = Frequency, Intensity, and Burden of Side Effects Rating
Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire
SAE/AE = Serious Adverse Events/Adverse Events Forms – as needed.
WPAI = The Work Productivity and Activity Impairment Scale
WSAS = Work and Social Adjustment Scale

CLINIC VISIT FORM:
RX = Study Medication Tracking form
SE = Side Effect Checklist
VS = Vital Signs (BP, P, weight, waist circumference)
XI. STRATIFICATION AND RANDOMIZATION

Patients who have been on an antidepressant at a stable “optimal” dose for at least three weeks and have not achieved improvement of symptoms (defined as QIDS-C16 ≥11 after eight weeks of treatment or QIDS-C16 ≥16 after six weeks of treatment) on the antidepressant regimen they were prescribed, and who meet all other inclusion and exclusion criteria, will be eligible to participate in the study. Only participants with nonpsychotic MDD who meet the study eligibility criteria and the QIDS-C16 criteria at the baseline assessment will be considered for randomization. Patients with a QIDS-C16 <10 at the baseline assessment will not be randomized and will continue to be treated by their treating physicians. The first study visit for eligible enrolled participants will be the Baseline /Randomization Visit where a clinical evaluation shall determine that the patient has not achieved an adequate response to the currently prescribed antidepressant and has not worsened to the degree that the patient is at high suicide risk or is in need of immediate hospitalization for depression.

Eligible patients who have consented to participate will be randomized to one of the three treatment strategies: switching from their current antidepressant to BUP-SR monotherapy, augmentation of their current antidepressant with BUP-SR, or augmentation of their current antidepressant with aripiprazole (see Section XIV). The treatment allocation ratio for the three treatment regimens will be 1:1:1 and will be stratified by medical center using a random permuted block scheme with variable block size. The random treatment scheme will be generated by the West Haven CSPCC (WH-CSPCC). When a subject is to be randomized, the Study Coordinator or Independent Evaluator will use a web-based Electronic Data Capture (EDC) system to complete the eligibility and baseline forms. The EDC website will require the site personnel to enter a user name and password to log on. Once the system has verified the user name and password, the Study Coordinator will confirm the patient’s eligibility by answering several questions on the Randomization Form. If all eligibility criteria are satisfied and informed consent has been obtained, a new randomization will be requested and the algorithm will assign a randomization number to the patient which will correspond to a treatment assignment to one of the three regimens. The treatment assignment will be reported immediately on the computer screen, and the screen will be printed for the patient’s study chart and recorded.
on the Randomization Form. The EDC system will also generate drug bottle number assignments that correspond to the treatment regimen assigned. The Albuquerque CSPCRPCC will be responsible for supplying the drugs. This procedure will be tested and validated before enrollment begins.

The WH-CSPCC will review the overall randomization at least weekly during the enrollment phase of the study and will be monitoring the randomization transactions on a daily basis. The unique study ID number will be linked in the randomization file to the treatment assignment for each randomized participant. The randomization file data will remain separate from the rest of the study data on the central database.

Randomization will occur on the same day that the patient has completed the necessary portions of the Screening and Baseline assessments, including the QIDS-C16, and is judged eligible for randomization. When a new participant has been randomized, his/her electronic medical record will be updated indicating participation in a research study. Source documentation for eligibility criteria and randomization will be kept at the site with the participant’s study folder.

Participating sites that are approved to enroll participants will be expected to randomize at least two participants per month until the targeted sample size of 1518 randomized participants has been reached. Once it has been confirmed by CSPCC that the target sample sized has been obtained, all active participating sites will be notified to stop enrolling new participants. However, randomization will still be offered to any enrolled participant if randomization can be completed before the end of the approved recruitment period. This may result in a small number of randomizations (less than 25) that exceed the target sample size.
XII. BLINDING OF THE RANDOMIZATION SCHEME

The randomization scheme will be kept blinded so that the allocation to treatments will be concealed as much as possible. All study investigators and study personnel will be blinded to the randomization scheme such that the allocation to study arms will be concealed. The variable block scheme will make it difficult to predict which treatment will be assigned next. However, once randomized, the study investigator and the patient will be aware of which treatment has been assigned. The independent evaluator (IE), who will be involved in recruitment and screening, will not be involved in the randomization process or the prescription of study medications. After randomization, the IE will only be involved in administering the QIDS-C\textsubscript{16} and other questionnaires that do not involve information about the treatment assignment or side effects. The IE will make every effort to remain blinded throughout the follow-up period; however, since the participant and other members of the study team are unblinded, it will be difficult for all assessments to be completed blinded to treatment assignment. Therefore, it will be documented on the QIDS-C\textsubscript{16} if an assessment is completed by an unblinded evaluator, but unblinded assessments will not be documented separately as protocol deviations. Back-up procedures will be established in the Study Operations Manual to cover the administering of the QIDS-C\textsubscript{16} in the event that the IE is not available. The back-up procedures will allow for trained Study Coordinators, back-up evaluators or central Lead Evaluator located at the Co-Chairs Office to administer the depression symptom questionnaires.

Since the monotherapy (switching) treatment regimen requires the discontinuing of the antidepressant that had been prescribed in prior to randomization, it is not feasible to blind the treatment assignments for the primary hypothesis. Additional rationale for not blinding the patients and physicians for the three active treatment strategies is addressed elsewhere in the protocol (Section VI).
XIII. FOLLOW-UP ASSESSMENT PROCEDURES

Follow-up visits will be conducted the first 2 weeks after randomization and then every two
weeks for the first twelve weeks following randomization and every four weeks subsequently
until patients have been followed for nine months post-randomization.

A. Assessments administered at each visit

At each visit, the primary outcome variable (QIDS-C16), global depression ratings, side effect
ratings and adherence measures will be assessed. In addition, the PHQ-9 will be administered to
help guide dosing.

<table>
<thead>
<tr>
<th>Table 5. Treatment Visit Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Domain</strong></td>
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<tr>
<td>Symptom</td>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
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<td>Safety</td>
</tr>
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</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Treatment Decisions</td>
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<td>Treatment</td>
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<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Medical History</td>
</tr>
<tr>
<td>Total Time</td>
</tr>
</tbody>
</table>

**CLINIC VISIT FORM:**
- AQ = Adherence Questionnaire
- RX = Study Medication Tracking form
- VS = Vital Signs (BP, P, weight)
- SE = Side Effect Checklist
- CGI-I = Clinical Global Impression - Improvement
- CGI-S = Clinical Global Impression- Severity
- CMT = Concomitant Medication Tracking form

**FIBSER** = Frequency, Intensity, and Burden of Side Effects Rating
**QIDS-C16** = 16-item Quick Inventory of Depressive Symptomatology - Clinician-report
**PHQ-9** = Patient Health Questionnaire
**SAE/AE** = Serious Adverse Events/Adverse Events Forms – as needed.
B. Assessments administered at baseline, at the end of acute treatment (12 weeks or sooner), at 24 weeks, and at the end of study (36 weeks or sooner) only

More comprehensive assessments will be administered prior to treatment (at baseline), after acute treatment (week 12 or sooner), at week 24, and after completion of the study (week 36 or sooner) (see Table 6). These assessments will include all of the treatment visit assessments plus additional measures of depression associated systems (anxiety and suicidal ideation), safety, quality of life, and health related costs. Approximately 1 tablespoon of blood will be drawn and submitted to the local laboratory for tests that will help monitor for possible side effects of medications, in particular, problems with kidney or liver function. These tests will include: cholesterol (total, HDL, LDL), triglycerides, glucose, platelets, WBC, RBC, hemoglobin, hematocrit, alanine transaminase (ALT) and creatinine. At the last visit, participant satisfaction with the study also will be assessed.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Measure</th>
<th>Time (Minutes)</th>
<th>How</th>
<th>Who</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated Symptoms</td>
<td>BAI</td>
<td>5</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td></td>
<td>C-SSRS</td>
<td>10</td>
<td>Interview</td>
<td>Study Coordinator/IE</td>
</tr>
<tr>
<td></td>
<td>PCL-5</td>
<td>5</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td></td>
<td>Mania/Hypomania</td>
<td>5</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td></td>
<td>Positive MH</td>
<td>3</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td>Safety</td>
<td>BAS</td>
<td>2</td>
<td>Exam</td>
<td>Study Coordinator</td>
</tr>
<tr>
<td></td>
<td>ASES</td>
<td>4</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td></td>
<td>Lab Studies</td>
<td>10</td>
<td>Blood draw</td>
<td>Study Coordinator</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>WSAS</td>
<td>2</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td></td>
<td>WPAI</td>
<td>3</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td></td>
<td>Q-LES-Q</td>
<td>6</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td></td>
<td>EQ-5D</td>
<td>3</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td>Health Costs</td>
<td>Income and Employment</td>
<td>2</td>
<td>Self-Report</td>
<td>Participant</td>
</tr>
<tr>
<td></td>
<td>Use of non-VA resources</td>
<td>2</td>
<td>Interview</td>
<td>Study Coordinator</td>
</tr>
<tr>
<td>Total Time</td>
<td></td>
<td>40-50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASES = Arizona Sexual Experience Scale  
PCL-5 = PTSD Checklist (if MINI = PTSD)  
BAI = Beck Anxiety Inventory  
Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire  
BAS = Barnes Akathisia Scale  
WPAI = The Work Productivity and Activity Impairment Scale  
C-SSRS = Columbia Suicide Severity Rating Scale  
WSAS = Work and Social Adjustment Scale  
EQ-5D = Euro Qol Health Questionnaire
XIV. TREATMENT REGIMENS

Participants may enter the study after a failed trial of any SSRI, SNRI or mirtazapine. We considered the pros and cons of allowing the study physician to select their medication of choice, based on the patient’s history, co-morbidities, clinical features, side effect profiles and preferences vs. limiting enrollment to patients on a specific medication or forcing participants to enter a lengthy run-in period with a specified antidepressant (see discussion on “why no run-in” above). The advantages of this approach are that it enhances generalizability of findings, as the more “liberal” method approaches the way medications are provided in the “real world”; facilitates recruitment of adequate participants as most physicians well favor this approach for most of their patients; is more consumer friendly as patients know their physician’s treatment choices are minimally proscribed and that they have a role in their own treatment decisions; and maximizes patient satisfaction as patients know they have received their physician’s treatment of choice. We felt the benefits of allowing the physician to enroll patients who have been given the medication they feel has the best chance of producing an optimal outcome for his/her patient far outweighed the benefits of forcing more narrow choices. The study is powered to answer the question of which treatment strategy is more effective for patients who have failed any SSRI, SNRI or mirtazapine - not just for those who have failed a specific antidepressant.

Participants will be randomized to one of three treatments: switching the antidepressant to BUP-SR augmenting the antidepressant with BUP-SR (antidep + BUP-SR) or augmenting the antidepressant with aripiprazole (antidep + ARI).

A. General Principles

The frequency of treatment visits is greater than typical practice and higher than often provided in the VA (i.e., weeks 1, 2, 4, 6, 8, 10 and 12), though the visit frequency is consistent with guidelines (AHCPR April 1993.). We chose a higher than usual frequency because (a) weekly to biweekly post-baseline visits are needed to safely yet appropriately titrate the combination treatments and (b) more frequent treatment visits should reduce attrition. Clinicians may substitute a telephone visit for a face-to-face visit at one occasion if patients are doing well and it is clinically acceptable. Additional visits are recommended for clinical worsening, emergent suicide ideation, or difficult to manage side effects. Dosing recommendations (see Table 7) are
consistent with VA/DoD, TMAP, STAR*D and APA guidelines (Crismon, Trivedi et al. 1999; Rush, Trivedi et al. 2006; Trivedi, Rush et al. 2006). Using “measurement based care” (Trivedi 2009) to guide dosing decisions, dose increments are carried out only in the context of balancing the goal of achieving remission with acceptable side effects and safety; the timing of the dose changes will vary across participants as deemed clinically appropriate. These dosing schedules are chosen to ensure vigorous delivery of medications while also assuring safety and tolerability.

B. Acute Treatment

As successfully implemented in the STAR*D trial (Trivedi 2009), the study physician will make treatment decisions guided by symptom ratings and side-effect frequency, intensity, burden, and tolerability, utilizing the measurements obtained at each visit medication visit. The goal of treatment is remission from of symptoms of MDD as measured by an endpoint QIDS-C16 ≤ 5. It is important to note that different symptom ratings are used to assess outcome (QIDS-C16) and to guide treatment (PHQ-9). At each visit, the physician should 1) assess the severity of the patient’s symptoms with the PHQ-9 and determine if an increase in medication is appropriate (e.g., for PHQ-9 ≥ 9, increase dose recommended; 5-8 may increase dose, based on study physician’s clinical judgment; ≤ 4 no change recommended), 2) assess the patient for tolerance with the FIBSER and make a decision to either continue or change treatment based on the patient’s ability to tolerate the medication (e.g., for FIBSER ≤ 4 increase dose as recommended by response; 5-7 additional assessment side effects and justify increase in dose; ≥8 dose increase not recommended – consider decrease dose, re-assessment in 1 week, other treatment or study exit).

- By Week 1, participants will be prescribed bupropion-SR 150 mg BID or aripiprazole 5 mg unless side effects prevent these doses.
- At subsequent visits, participants with PHQ-9 ≥ 5 may have their medication increased up to the maximum allowable dose or be maintained at the same dosage, assuming side effects are not problematic and remission has not been achieved.
- As early as Week 4, participants may have had their study medication increased up to the maximum allowable dose.
- Participants with PHQ-9 ≤ 4 may be maintained at the same dosage assuming side effects are not problematic.
• Participants experiencing intolerable side effects will have the medication dosage decreased, side effects managed and continue or exit the study. Patients experiencing tolerable side effects may have the medication dosage decreased, or continue the current dose and the side effects managed.
• Treatment of secondary symptoms (see below)

B.1. Switching to BUP-SR:
BUP-SR was chosen as the switching option because of its wide use and demonstrated effectiveness (Zisook, Rush et al. 2006). The most common side effects are constipation, dry mouth, headaches, insomnia and nausea.

The strategy for switching to BUP-SR will be to cross taper over a period of days to weeks, adding BUP-SR 150 mg while beginning to lower the dose of the index antidepressant. The speed of the taper will depend on the specific medication (e.g., slower for short acting medications like paroxetine and venlafaxine) and on dosage. Depending on response and tolerability (see above), BUP-SR usually will be increased to 150 mg BID at week 1. When the dose is not increased, reasons for maintaining the lower dose will be noted in the case report forms. Again, depending on response and tolerability, the dose may be increased up to its maximal dose of 400 mg per day (200 mg BID) as early as week 4.

The decision to allow such broad flexibility in the cross taper takes into account our intent to mimic actual care practices as much as possible to ensure that results will be applicable to “real” patients in “real” VA settings. We also feel this pragmatic cross tapering strategy provides optimal care and patient safety without compromising our ability to meet our study aims or test our hypotheses.

B.2. Augmenting with BUP-SR:
BUP-SR was chosen as the antidepressant for augmenting because of its wide use and demonstrated efficacy and tolerability (Zisook, Rush et al. 2006). In addition, using BUP-SR as both the switching agent and one of the augmentation agents facilitates direct comparison of switching vs. augmenting effectiveness. BUP-SR, a dopamine and norepinephrine modulator (Stahl, Pradko et al. 2004) is widely used to augment SSRIs or VEN, and is preferred

The strategy for augmenting with BUP-SR is to maintain the dose of the index antidepressant unless side effects (e.g., FIBSER > 5) warrant a lower dose while introducing BUP-SR. The starting dose of BUP-SR is 150 mg daily, generally given in the morning. Depending on response and tolerability (see above), BUP-SR usually will be increased to 150 mg BID at week 1. Again, depending on response and tolerability, it may be increased up to its maximal dose of 400 mg per day (200 mg BID) as early as week 4.

For side effect management, the physician can choose to lower the dose of BUP-SR or the index antidepressant based on clinical judgment. If for example, insomnia or headaches emerge only after starting or increasing the dose of BUP-SR, a reasonable clinical judgment would be to lower the dose of BUP-SR; if fatigue or sexual difficulties worsen after adding BUP-SR, lowering the dose of the other medication may be a reasonable strategy. Because of possible clinically meaningful drug interactions with venlafaxine (BUP-SR is a 2D6 inhibitor) possibly resulting in hypertension, special caution will be exercised with this combination and blood pressure will be closely monitored.

The decision to allow such broad flexibility in the dosing strategy takes into account our intent to mimic actual care practices as much as possible to ensure that results will be applicable to “real” patients in “real” VA settings. We also feel this pragmatic approach to adding one antidepressant to another, and to allowing clinical judgment to help guide subsequent dosing decisions of each of the antidepressants will serve to maximize efficacy and adherence while minimizing side effects. This strategy is meant to provide optimal care and patient safety without compromising our ability to meet our study aims or test our hypotheses.
B.3. Augmenting with ARI:

ARI was chosen as the antipsychotic for switching because it is the first FDA approved SGA augmenting agent and because of its demonstrated efficacy (at least for acute, short term treatment) (Patkar, Peindl et al. 2006; Berman, Marcus et al. 2007; Pae, Patkar et al. 2007; Hellerstein, Batchelder et al. 2008; Marcus, McQuade et al. 2008). The most common side effects are agitation, constipation, extrapyramidal symptoms, insomnia, nausea and somnolence.

The strategy for augmenting with ARI is to maintain the dose of the index medication unless side effects (e.g., FIBSER ≥ 5) warrant a lower dose while introducing ARI. The starting dose of ARI is 2 mg daily, generally given in the morning. Depending on response and tolerability (see Table 7), ARI usually will be increased to 5 mg at week 1. At week 2, depending on response and tolerability, ARI will be increased to 10 mg. Again, depending on response and tolerability, it may be increased up to its maximal dose of 15 mg daily as early as week 4.

For side effect management, the physician can chose to lower the dose of ARI or of the concomitant antidepressant based on clinical judgment. If for example, tremors emerge only after starting or increasing the dose of ARI, a reasonable clinical judgment would be to lower the dose of ARI; if diarrhea worsens after adding ARI, lowering the dose of the other medication may be a reasonable strategy.

As noted in the discussion of the rationale for allowing such a flexible dosing strategy with bupropion-SR augmentation, this dosing strategy takes into account our intent to mimic actual care practices as much as possible to ensure that results will be applicable to “real” patients in “real” VA settings. We also feel this pragmatic approach to adding one aripiprazole to an antidepressant, and to allowing clinical judgment to help guide subsequent dosing decisions of each of the medications will serve to maximize efficacy and adherence while minimizing side effects. This strategy is meant to provide optimal care and patient safety without compromising our ability to meet our study aims or test our hypotheses.
C. Continuation Treatment

The goals of treatment are not only to get a patient well, but also to keep them well. It is well accepted that treatment must be maintained for at least several months beyond symptomatic remission (the “continuation” phase of treatment) to maximize the chance for functional recovery and to prevent relapse (Miller, Keitner et al. 1998; Judd, Paulus et al. 2000). Thus, it is critical to examine the effectiveness and safety of medications for at least 6 months beyond remission. As is standard care and recommended by all treatment guidelines (Crismon, Trivedi et al. 1999; APA 2000) the continuation phase doses will be the same as the doses used to achieve response or remission. At week 12, participants who have a QIDS-C16 ≥ 11 will exit the treatment protocol, be terminated from the study and be treated openly by their clinical provider. Those who have a QIDS-C16 of 9 or 10 may enter the continuation phase if they do not want to change medications, are satisfied with their response, and their study physician feels it is a reasonable decision. All participants with a QIDS-C16 ≤ 8 will be encouraged to remain in the continuation phase treatment. During this phase, visits with the treating physician are monthly.
### Table 7A. Guidelines for Treatment Decisions at Each Visit for Each Treatment:

**SWITCHING TO BUPROPION SR (BUP-SR)**

<table>
<thead>
<tr>
<th>Week 0</th>
<th>BUP-SR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Begin taper of antidepressant over 1-4 weeks as clinically indicated</td>
</tr>
<tr>
<td></td>
<td>Start bupropion SR dose at 150mg/day.</td>
</tr>
<tr>
<td>Return to clinic:</td>
<td>Return in 1 week.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 1</th>
<th>BUP-SR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increase Bupropion SR dose up to 300 mg/day. †</td>
</tr>
<tr>
<td>SEs are significant*</td>
<td>Continue current dose and manage SEs.</td>
</tr>
<tr>
<td>SEs are intolerable*</td>
<td>Manage SE and continue for 1 week or Exit if SE is not manageable.</td>
</tr>
<tr>
<td>Return to clinic:</td>
<td>Return in 1 week.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 2</th>
<th>BUP-SR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Continue Bupropion SR</td>
</tr>
<tr>
<td>SEs are significant*</td>
<td>Continue current dose and manage SE; or Decrease dose, manage SE and continue for 2 weeks.</td>
</tr>
<tr>
<td>SEs are intolerable*</td>
<td>Decrease dose, manage SE and continue for 2 weeks; or Exit if SE is not manageable.</td>
</tr>
<tr>
<td>Return to clinic:</td>
<td>Return in 2 weeks.</td>
</tr>
</tbody>
</table>

#### Week 4

**Symptom Improvement (SEs tolerable):**

| PHQ-9 ≥ 9 | Increase bupropion SR dose up to 400mg/day. † |
| PHQ-9 = 5-8 | Increase bupropion SR dose up to 400mg/day † or Continue current dose. |
| PHQ-9 ≤ 4 | Continue current dose. |
| SEs are significant* | Continue current dose and manage SE; or Decrease dose, manage SE and continue for 2 weeks. |
| SEs are intolerable* | Decrease dose, manage SE and continue for 2 weeks; or Exit if SE is not manageable. |
| Return to clinic: | Return in 2 weeks. |

#### Week 6

**Symptom Improvement (SEs tolerable):**

| PHQ-9 ≥ 9 | Increase bupropion SR dose up to 400mg/day. † |
| PHQ-9 = 5-8 | Increase bupropion SR dose up to 400mg/day † or Continue current dose. |
| PHQ-9 ≤ 4 | Continue current dose. |
| SEs are significant* | Continue current dose and manage SE; or Decrease dose, manage SE and continue for 2 weeks. |
| SEs are intolerable* | Decrease dose, manage SE and continue for 2 weeks; or Exit if SE is not manageable. |
| Return to clinic: | Return in 2 weeks. |

#### Week 8

**Symptom Improvement (SEs tolerable):**

| PHQ-9 ≥ 9 | Increase bupropion SR dose up to 400mg/day. †* |
| PHQ-9 = 5-8 | Increase bupropion SR dose up to 400mg/day † or Continue current dose. |
| PHQ-9 ≤ 4 | Continue current dose. |
| SEs are significant* | Continue current dose and manage SE; or Decrease dose, manage SE and continue for 2 weeks. |
| SEs are intolerable* | Decrease dose, manage SE and continue for 2 weeks; or Exit if SE is not manageable. |
| Return to clinic: | Return in 2 weeks. |
### WEEK 10 BUP-SR

<table>
<thead>
<tr>
<th>Symptom Improvement (SEs tolerable):</th>
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</thead>
<tbody>
<tr>
<td><strong>PHQ-9 ≥ 9</strong></td>
<td>Increase bupropion SR dose up to 400mg/day. †*&lt;br&gt;<strong>PHQ-9 = 5-8</strong></td>
</tr>
</tbody>
</table>

**SEs are significant***<br>Continue current dose and manage SE; or Decrease dose, manage SE and continue for 2 weeks.<br>**SEs are intolerable***<br>Decrease dose, manage SE and continue for 2 weeks; or Exit if SE is not manageable.<br>Return to clinic: Return in 2 weeks.

### WEEK 12 BUP-SR

<table>
<thead>
<tr>
<th>Symptom Improvement (SEs tolerable):</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>If QIDS-C&lt;sub&gt;16&lt;/sub&gt; ≥ 11</td>
<td>Exit treatment protocol.</td>
</tr>
<tr>
<td>If QIDS-C&lt;sub&gt;16&lt;/sub&gt; = 9 or 10</td>
<td>May enter Continuation Phase Treatment. If so, may increase bupropion SR dose up to 400mg/day † following PHQ-9 guidelines.</td>
</tr>
<tr>
<td>If QIDS-C&lt;sub&gt;16&lt;/sub&gt; ≤ 8</td>
<td>Enter Continuation Phase Treatment. If so, may increase bupropion SR dose up to 400mg/day † following PHQ-9 guidelines.</td>
</tr>
</tbody>
</table>

**SEs are significant***<br>Continue current dose and manage SE; or Decrease dose, manage SE and continue for 2 weeks.<br>**SEs are intolerable***<br>Decrease dose, manage SE and continue for 2 weeks; or Exit if SE is not manageable.<br>Return to clinic: In 4 weeks if medication has not been changed during clinic visit or in 2 weeks if medication has been changed during clinic visit or side effects have been severe.

### WEEKS 16, 20, 24, 28, 32 †† BUP-SR

<table>
<thead>
<tr>
<th>Symptom Improvement (SEs tolerable):</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PHQ-9 ≥ 9</strong></td>
<td>Increase bupropion SR dose up to 400mg/day. †&lt;br&gt;<strong>PHQ-9 = 5-8</strong></td>
</tr>
</tbody>
</table>

**SEs are significant***<br>Continue current dose and manage SE; or Decrease dose, manage SE and continue for 2 weeks.<br>**SEs are intolerable***<br>Decrease dose, manage SE and continue for 2 weeks; or Exit if SE is not manageable.<br>Return to clinic: In 4 weeks if medication has not been changed during clinic visit or in 2 weeks if medication has been changed during clinic visit or side effects have been severe.

---

* Use the FIBSER as a guide: ≤ 4 increase dose as recommended by response; 5-7 additional assessment of side effects and justify increase in dose; ≥ 8 dose increase not recommended – consider decrease dose, re-assessment in 1 week, other treatment or study exit.<br>† Increase bupropion SR dose to 300 mg/day if current dose is 150 mg/day or increase to 400 mg/day if current dose is 300 mg/day. Clinician should consider any possible drug interactions or contraindications with current antidepressant medication when making dose change decisions.<br>†† All participants exit by Week 36 and return to usual care; therefore no Week 36 grids are provided.<br>◦ Participants who are not improving by Weeks 8 or 10, as measured by the PHQ ≥ 9 or QIDS-C<sub>16</sub> ≥ 11 may be considered for early termination due to clear lack of treatment efficacy and need for next-step treatment.
### Guidelines for Treatment Decisions at Each Visit for Each Treatment: AUGMENTING WITH BUPROPION SR (ANTI + BUP-SR)

<table>
<thead>
<tr>
<th>Week 0</th>
<th>ANTI + BUP-SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return to clinic:</td>
<td>Return in 1 week.</td>
</tr>
<tr>
<td><strong>Start bupropion SR dose at 150mg/day.</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 1</th>
<th>ANTI + BUP-SR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increase Bupropion SR dose up to 300 mg/day†.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>SEs are significant</strong>*</td>
<td>Continue current dose and manage SEs.</td>
</tr>
<tr>
<td><strong>SEs are intolerable</strong>*</td>
<td>Manage SE and continue for 1 week; or Exit if SE is not manageable.</td>
</tr>
<tr>
<td>Return to clinic:</td>
<td>Return in 1 week.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 2</th>
<th>ANTI + BUP-SR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continue current dose and manage SE or Decrease dose (of either or both antidepressants), manage SE and continue for 2 weeks.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>SEs are significant</strong>*</td>
<td>Decrease dose (of either or both antidepressants), manage SE and continue for 2 weeks; or Exit if SE is not manageable.</td>
</tr>
<tr>
<td><strong>SEs are intolerable</strong>*</td>
<td>Decrease dose (of either or both antidepressants), manage SE and continue for 2 weeks; or Exit if SE is not manageable.</td>
</tr>
<tr>
<td>Return to clinic:</td>
<td>Return in 2 weeks.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 4</th>
<th>ANTI + BUP-SR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom Improvement (SEs tolerable):</strong></td>
<td></td>
</tr>
<tr>
<td><strong>PHQ-9 ≥ 9</strong></td>
<td>Increase bupropion SR dose up to 400mg/day.†</td>
</tr>
<tr>
<td><strong>PHQ-9 = 5-8</strong></td>
<td>Increase bupropion SR dose up to 400mg/day† or Continue current dose.</td>
</tr>
<tr>
<td><strong>PHQ-9 &lt; 4</strong></td>
<td>Continue current dose.</td>
</tr>
<tr>
<td><strong>SEs are significant</strong>*</td>
<td>Continue current dose and manage SE or Decrease dose (of either or both antidepressants), manage SE and continue for 2 weeks.</td>
</tr>
<tr>
<td><strong>SEs are intolerable</strong>*</td>
<td>Decrease dose (of either or both antidepressants), manage SE and continue for 2 weeks; or Exit if SE is not manageable.</td>
</tr>
<tr>
<td>Return to clinic:</td>
<td>Return in 2 weeks.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 6</th>
<th>ANTI + BUP-SR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom Improvement (SEs tolerable):</strong></td>
<td></td>
</tr>
<tr>
<td><strong>PHQ-9 ≥ 9</strong></td>
<td>Increase bupropion SR dose up to 400mg/day.†</td>
</tr>
<tr>
<td><strong>PHQ-9 = 5-8</strong></td>
<td>Increase bupropion SR dose up to 400mg/day† or Continue current dose.</td>
</tr>
<tr>
<td><strong>PHQ-9 &lt; 4</strong></td>
<td>Continue current dose.</td>
</tr>
<tr>
<td><strong>SEs are significant</strong>*</td>
<td>Continue current dose and manage SE or Decrease dose (of either or both antidepressants), manage SE and continue for 2 weeks.</td>
</tr>
<tr>
<td><strong>SEs are intolerable</strong>*</td>
<td>Decrease dose (of either or both antidepressants), manage SE and continue for 2 weeks; or Exit if SE is not manageable.</td>
</tr>
<tr>
<td>Return to clinic:</td>
<td>Return in 2 weeks.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 8</th>
<th>ANTI + BUP-SR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom Improvement (SEs tolerable):</strong></td>
<td></td>
</tr>
<tr>
<td><strong>PHQ-9 ≥ 9</strong></td>
<td>Increase bupropion SR dose up to 400mg/day.†</td>
</tr>
<tr>
<td><strong>PHQ-9 = 5-8</strong></td>
<td>Increase bupropion SR dose up to 400mg/day† or Continue current dose.</td>
</tr>
<tr>
<td><strong>PHQ-9 &lt; 4</strong></td>
<td>Continue current dose.</td>
</tr>
<tr>
<td><strong>SEs are significant</strong>*</td>
<td>Continue current dose and manage SE or Decrease dose (of either or both antidepressants), manage SE and continue for 2 weeks.</td>
</tr>
<tr>
<td><strong>SEs are intolerable</strong>*</td>
<td>Decrease dose (of either or both antidepressants), manage SE and continue for 2 weeks; or Exit if SE is not manageable.</td>
</tr>
<tr>
<td>Return to clinic:</td>
<td>Return in 2 weeks.</td>
</tr>
</tbody>
</table>
**WEEK 10**  
**ANTI + BUP-SR**

### Symptom Improvement (SEs tolerable):

| PHQ-9 ≥ 9 | Increase bupropion SR dose up to 400mg/day †* |
| PHQ-9 = 5-8 | Increase bupropion SR dose up to 400mg/day † or Continue current dose. |
| PHQ-9 ≤ 4 | Continue current dose. |

**SEs are significant***  
Continue current dose and manage SE or Decrease dose (of either or both antidepressants), manage SE and continue for 2 weeks.

**SEs are intolerable***  
Decrease dose (of either or both antidepressants), manage SE and continue for 2 weeks; or Exit if SE is not manageable.

Return to clinic: Return in 2 weeks.

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**WEEK 12**  
**ANTI + BUP-SR**

### Symptom Improvement (SEs tolerable):

If QIDS-C16 ≥ 11  
Exit treatment protocol.  
May enter Continuation Phase Treatment. If so, may increase bupropion SR dose up to 400mg/day † or continue current dose.

If QIDS-C16 = 9 or 10  
Enter Continuation Phase Treatment. If QIDS-C 6-8 increase bupropion SR dose up to 400mg/day † or continue current dose. If QIDS-C ≤ 5, continue current dose.

If QIDS-C16 ≤ 8  
Continue current dose and manage SE or Decrease dose (of either or both antidepressants), manage SE and continue for 2 weeks.

**SEs are significant***  
Continue current dose and manage SE or Decrease dose (of either or both antidepressants), manage SE and continue for 2 weeks.

**SEs are intolerable***  
Decrease dose (of either or both antidepressants), manage SE and continue for 2 weeks; or Exit if SE is not manageable.

Return to clinic: In 4 weeks if medication has not been changed during clinic visit or in 2 weeks if medication has been changed during clinic visit or side effects have been severe.

---

**WEEKS 16, 20, 24, 28, 32 ††**  
**ANTI + BUP-SR**

### Symptom Improvement (SEs tolerable):

| PHQ-9 ≥ 9 | Increase bupropion SR dose up to 400mg/day † |
| PHQ-9 = 5-8 | Increase bupropion SR dose up to 400mg/day † or Continue current dose. |
| PHQ-9 ≤ 4 | Continue current dose. |

**SEs are significant***  
Continue current dose and manage SE or Decrease dose (of either or both antidepressants), manage SE and continue for 2 weeks.

**SEs are intolerable***  
Decrease dose (of either or both antidepressants), manage SE and continue for 2 weeks; or Exit if SE is not manageable.

Return to clinic: In 4 weeks if medication has not been changed during clinic visit or in 2 weeks if medication has been changed during clinic visit or side effects have been severe.

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* Use the FIBSER as a guide: ≤4 increase dose as recommended by response; 5-7 additional assessment of side effects and justify increase in dose; ≥8 dose increase not recommended – consider decrease dose, re-assessment in 1 week, other treatment or study exit.

† Increase bupropion SR dose to 300 mg/day if current dose is 150 mg/day or increase to 400 mg/day if current dose is 300 mg/day. Clinician should consider any possible drug interactions or contraindications with current antidepressant medication when making dose change decisions.

†† All participants exit by Week 36 and return to usual care; therefore no Week 36 grids are provided.

Participants who are not improving by Weeks 8 or 10, as measured by the PHQ ≥ 9 or QIDS-C16 ≥ 11 may be considered for early termination due to clear lack of treatment efficacy and need for next-step treatment.
Table 7C. Guidelines for Treatment Decisions at Each Visit for Each Treatment:
AUGMENTING WITH ARIPIPRAZOLE (ANTI + ARI)

<table>
<thead>
<tr>
<th>Week</th>
<th>Treatment</th>
<th>Action/Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WEEK 0</strong></td>
<td>ANTI + ARI</td>
<td><strong>Start aripiprazole dose at 2mg/day.</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Return to clinic:</strong> Return in 1 week.</td>
</tr>
<tr>
<td><strong>WEEK 1</strong></td>
<td>ANTI + ARI</td>
<td>May Increase aripiprazole dose up to 5 mg/day.</td>
</tr>
<tr>
<td>SEs are significant*</td>
<td>Continue current dose and manage SEs.</td>
<td></td>
</tr>
<tr>
<td>SEs are intolerable*</td>
<td>Decrease dose, manage SE and continue for 1 week; or Exit if SE is not manageable.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Return to clinic: Return in 1 week.</td>
<td></td>
</tr>
<tr>
<td><strong>WEEK 2</strong></td>
<td>ANTI + ARI</td>
<td>May Increase aripiprazole dose up to 10 mg/day</td>
</tr>
<tr>
<td>SEs are significant*</td>
<td>Continue current dose and manage SE or Decrease dose (of either or both medications), manage SE and continue for 2 weeks.</td>
<td></td>
</tr>
<tr>
<td>SEs are intolerable*</td>
<td>Decrease dose (of either or both medications), manage SE and continue for 2 weeks; or Exit if SE is not manageable.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Return to clinic: Return in 2 weeks.</td>
<td></td>
</tr>
<tr>
<td><strong>WEEK 4</strong></td>
<td>ANTI + ARI</td>
<td>Symptom Improvement (SEs tolerable):</td>
</tr>
<tr>
<td>PHQ-9 &gt; 9</td>
<td>Increase aripiprazole dose up to 15mg/day.†</td>
<td></td>
</tr>
<tr>
<td>PHQ-9 = 5-8</td>
<td>Increase aripiprazole dose up to 15mg/day † or Continue current dose.</td>
<td></td>
</tr>
<tr>
<td>PHQ-9 &lt; 4</td>
<td>Continue current dose.</td>
<td></td>
</tr>
<tr>
<td>SEs are significant*</td>
<td>Continue current dose and manage SE or Decrease dose (of either or both medications), manage SE and continue for 2 weeks.</td>
<td></td>
</tr>
<tr>
<td>SEs are intolerable*</td>
<td>Decrease dose (of either or both medications), manage SE and continue for 2 weeks; or Exit if SE is not manageable.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Return to clinic: Return in 2 weeks.</td>
<td></td>
</tr>
<tr>
<td><strong>WEEK 6</strong></td>
<td>ANTI + ARI</td>
<td>Symptom Improvement (SEs tolerable):</td>
</tr>
<tr>
<td>PHQ-9 &gt; 9</td>
<td>Increase aripiprazole dose up to 15mg/day.†</td>
<td></td>
</tr>
<tr>
<td>PHQ-9 = 5-8</td>
<td>Increase aripiprazole dose up to 15mg/day † or Continue current dose.</td>
<td></td>
</tr>
<tr>
<td>PHQ-9 &lt; 4</td>
<td>Continue current dose.</td>
<td></td>
</tr>
<tr>
<td>SEs are significant*</td>
<td>Continue current dose and manage SE or Decrease dose (of either or both medications), manage SE and continue for 2 weeks.</td>
<td></td>
</tr>
<tr>
<td>SEs are intolerable*</td>
<td>Decrease dose (of either or both medications), manage SE and continue for 2 weeks; or Exit if SE is not manageable.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Return to clinic: Return in 2 weeks.</td>
<td></td>
</tr>
<tr>
<td><strong>WEEK 8</strong></td>
<td>ANTI + ARI</td>
<td>Symptom Improvement (SEs tolerable):</td>
</tr>
<tr>
<td>PHQ-9 &gt; 9</td>
<td>Increase aripiprazole dose up to 15mg/day.†*</td>
<td></td>
</tr>
<tr>
<td>PHQ-9 = 5-8</td>
<td>Increase aripiprazole dose up to 15mg/day † or Continue current dose.</td>
<td></td>
</tr>
<tr>
<td>PHQ-9 &lt; 4</td>
<td>Continue current dose.</td>
<td></td>
</tr>
<tr>
<td>SEs are significant*</td>
<td>Continue current dose and manage SE or Decrease dose (of either or both medications), manage SE and continue for 2 weeks.</td>
<td></td>
</tr>
<tr>
<td>SEs are intolerable*</td>
<td>Decrease dose (of either or both medications), manage SE and continue for 2 weeks; or Exit if SE is not manageable.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Return to clinic: Return in 2 weeks.</td>
<td></td>
</tr>
</tbody>
</table>
### Week 10

#### Symptom Improvement (SEs tolerable):  

| PHQ-9 ≥ 9  | Increase aripiprazole dose up to 15mg/day.†  
| PHQ-9 = 5-8 | Increase aripiprazole dose up to 15mg/day † or Continue current dose.  
| PHQ-9 < 4  | Continue current dose.  

#### SEs are significant*  

- Continue current dose and manage SE or Decrease dose (of either or both medications), manage SE and continue for 2 weeks.  

#### SEs are intolerable*  

- Decrease dose (of either or both medications), manage SE and continue for 2 weeks; or Exit if SE is not manageable.  

**Return to clinic:**  

- Return in 2 weeks.  

### Week 12

#### Symptom Improvement (SEs tolerable):  

| QIDS-C16 ≥ 11 | Exit treatment protocol  
| Ir QIDS-C16 = 9 or 10 | May enter Continuation Phase Treatment. If so, increase aripiprazole dose up to 15mg/day † or continue current dose.  
| Ir QIDS-C16 ≤ 8 | Move to Continuation Phase Treatment. If QIDS-C 6-8 increase aripiprazole dose up to 15mg/day † or continue current dose. If QIDS-C ≤ 5, continue current dose.  

#### SEs are significant*  

- Decrease dose (of either or both medications), manage SE and continue for 2 weeks.  

#### SEs are intolerable*  

- Decrease dose (of either or both medications), manage SE and continue for 2 weeks; or Exit if SE is not manageable.  

**Return to clinic:**  

- In 4 weeks if medication has not been changed during clinic visit or in 2 weeks if medication has been changed during clinic visit or side effects have been severe.  

### Weeks 16, 20, 24, 28, 32 ††  

#### Symptom Improvement (SEs tolerable):  

| PHQ-9 ≥ 9  | Increase aripiprazole dose up to 15mg/day.†  
| PHQ-9 = 5-8 | Increase aripiprazole dose up to 15mg/day † or Continue current dose.  
| PHQ-9 < 4  | Continue current dose.  

#### SEs are significant*  

- Continue current dose and manage SE or Decrease dose (of either or both medications), manage SE and continue for 2-4 weeks.  

#### SEs are intolerable*  

- Decrease dose (of either or both medications), manage SE and continue for 2 weeks; or Exit if SE is not manageable.  

**Return to clinic:**  

- In 4 weeks if medication has not been changed during clinic visit or in 2 weeks if medication has been changed during clinic visit or side effects have been severe.  

---

* Use the FIBSER as a guide: ≤ 4 increase dose as recommended by response; 5-7 additional assessment of side effects and justify increase in dose; ≥ 8 dose increase not recommended – consider decrease dose, re-assessment in 1 week, other treatment or study exit.†  

† Increase aripiprazole dose to 15 mg/day if current dose is 10 mg/day, or increase to 10 mg/day if current dose is 5 mg/day or increase to 5 mg/day if current dose is 2 mg/day. Clinician should consider any possible drug interactions or contraindications with current antidepressant medication when making dose change decisions.  

†† All participants exit by Week 36 and return to usual care; therefore no Week 36 grids are provided.  

○ Participants who are not improving by Weeks 8 or 10, as measured by the PHQ ≥ 9 or QIDS-C16 ≥ 11 may be considered for early termination due to clear lack of treatment efficacy and need for next-step treatment.
D. Concomitant Medications and Treatments

Patients taking exclusionary medications may become eligible for the study if it is clinically indicated to taper them off of the exclusionary medication and initiate a different protocol-permissible medication (as clinically indicated). The washout period is at least 5 days, participants must not take exclusionary medications for at least 5 days prior to the baseline visit.

D.1. Treatments for Depression: Only protocol medication treatments for depression are allowed. If any additional depression-targeted treatments are needed during study participation, participants will be exited from the study, the exit reasons will be recorded, and the participant will be referred back to his/her personal clinician to continue treatment for depression.

Potential depression-treatment augmenting agents (e.g., T3 in the absence of thyroid disease, SAMe (S-adenosyl-methionine), St. John’s Wort, lithium and buspirone) are exclusions for study participation and proscribed during study participation, as are somatic therapies (e.g., rTMS, VNS, ECT), specified anticonvulsants and mood stabilizers. Some low dose antidepressants and anxiolytics are allowed to treat symptoms other than depression. See Section D.4 below for examples, exclusions and exceptions.

Therapies such as supportive, couples, or occupational therapy are allowed at any time while participants are enrolled in the study. Patients currently enrolled in a depression-targeted, empirically validated psychotherapy (e.g., cognitive, interpersonal, behavioral, brief psychodynamic therapy) at the time of consent, who otherwise meet study inclusion/exclusion criteria are eligible to enter the study; however, despite research showing psychotherapy plus medication is better than either psychotherapy or medication alone, initiating any depression-targeted, empirically validated psychotherapy after consent is proscribed as this may confound our efforts to compare the acute and longer-term antidepressant effects of the protocol treatments. LSIs are encouraged to consult Study Chairs with questions about potentially proscribed psychotherapies.

We will record all treatments received (psychotherapeutic, alternating somatic, psychopharmacological) during the acute and longer-term phases. If a depression-targeted,
empirically validated psychotherapy or depression-targeted medication regimen is initiated during the study, the participant may be withdrawn from the study.

**D.2. Treatments for General Medical Conditions (GMC):**
Any treatment for any GMC is allowed.

**D.3. Treatments for Antidepressant Medication Side Effects:**
Medications to treat antidepressant medication side effects are allowed to mimic practice and increase retention. The most common side effects are likely to be sexual dysfunction, anxiety, or insomnia and may be treated using the following guidelines or at the LSI’s discretion:

- **Anxiety/Agitation.** Treatment emergent anxiety may be treated by watchful waiting/support, protocol medication dose adjustment, or, if necessary, a benzodiazepine such as clonazepam (0.5 to 2.0 mg/day) or lorazepam 0.5-2.0 mg/day.

- **Insomnia.** Insomnia may be treated by watchful waiting/support, protocol medication dose adjustment, sleep hygiene or a hypnotic such as zolpidem 5-10 mg qhs, eszopiclone 1-3 mg qhs, a benzodiazepine hypnotic (e.g. temazepam 15-30 mg qhs) or trazodone (up to 100 mg qhs) at clinician discretion.

- **Sexual dysfunction.** Phosphodiesterase (PDE) inhibitors (e.g., sildenafil 50-100 mg prn; tadalafil 5-20 mg prn) may be used to treat treatment-emergent sexual dysfunction as clinically dictated.

While the treatments listed above are intended to be guidelines, the medication ranges listed above do reflect the dose ceilings allowed in the study for these particular medications. Medications in the same class or dose levels as those listed above may also be used at the LSI’s discretion. The important issue is to treat emergent side effects safely and effectively to maximize patient comfort and study retention. LSIs are encouraged to consult Study Chairs with questions about treatments for emergent antidepressant side effects.

**D.4. Psychotropic Medication Treatments for Conditions Other Than Depression**
Use of anxiolytics for anxiety, hypnotic-sedatives for insomnia, or phosphodiesterase inhibitors for sexual dysfunction are permissible for study entry. Dose ceilings are the same for study entry.
as they are for the treatment of emergent side effects. See Section D.3 (above) for allowable
dose ceilings. The use of Ritalin or Adderall for ADD/ADHD is also permissible for study entry.

Low dose antidepressants targeted for symptoms other than depression (for example, the
tetracyclic antidepressant trazodone at $\leq 100$ mg for sleep, or the tricyclic antidepressant
amitriptyline at $\leq 75$ mg for pain) may be allowed on a case by case basis after discussion with
the LSI along with documentation that 1) the medication is not targeted for depression and 2) the
LSI feels the addition of study medications would be safe and clinically reasonable. Note that
quetiapine (Seroquel) cannot be used at any time during study participation, even for insomnia.
Allowable antidepressants and their acceptable maximum dose for conditions other than MDD
(e.g., sleep, fibromyalgia, pain, etc.) include:

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Maximum Allowable Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>imipramine</td>
<td>Tofranil</td>
<td>An average of $\leq 100$ mg/day</td>
</tr>
<tr>
<td>amitriptyline</td>
<td>Elavil, Endep</td>
<td>An average of $\leq 100$ mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>($\leq 75$ mg/day for pain)</td>
</tr>
<tr>
<td>clomipramine</td>
<td>Anafranil</td>
<td>An average of $\leq 100$ mg/day</td>
</tr>
<tr>
<td>doxepin</td>
<td>Sinequan, Adapin</td>
<td>An average of $\leq 100$ mg/day</td>
</tr>
<tr>
<td>desipramine</td>
<td>Norpramin</td>
<td>An average of $\leq 100$ mg/day</td>
</tr>
<tr>
<td>nortriptyline</td>
<td>Pamelo</td>
<td>An average of $\leq 50$ mg/day</td>
</tr>
<tr>
<td>trazodone</td>
<td>Desyrel</td>
<td>An average of $\leq 100$ mg/day</td>
</tr>
</tbody>
</table>

If a patient is taking any other potential augmenting agent not mentioned in this list, LSIs are
asked to contact the Study Chairs prior to randomization to discuss the patient’s eligibility.

All antipsychotics, regardless of dose or purpose, are excluded from study procedures. However,
potential participants taking a low dose antipsychotic such as quetiapine (Seroquel) for sleep, for
example, may become eligible if they can be switched to another permissible sleep treatment
(see washout procedures above).

Patients taking anticonvulsants/mood stabilizers that fall into the family of the medications listed
in the table below are **not** eligible to participate and must be excluded from randomization:
Other anticonvulsants (except those with mood stabilizing properties), including but not limited
to gabapentin or topiramate, are permissible as adjunctive medication in the study.

Adjunct mirtazapine is proscribed, regardless of the indication, dose or duration of use; however,
mirtazapine monotherapy is allowed for study entry, with mirtazapine as the index antidepressant.

D.5. Medications Contraindicated for Bupropion-SR or Aripiprazole Treatment

Bupropion-SR is contraindicated in participants treated with medications containing bupropion,
such as Zyban (bupropion hydrochloride), Wellbutrin (bupropion) or Wellbutrin XL (bupropion)
and in participants treated with an MAOI (monoamine oxidase inhibitor), such as Marplan
(isocarboxazid), Manerix (moclobemide), Nardil (phenelzine), Parnate (tranylcypromine), or
EMSAM (selegilene transdermal system).

Special care should be taken with respect to titration of study drug in participants taking
centrally-acting drugs and/or inhibitors of CYP3A4 (e.g. ketoconazole or carbamazepine) or
CYP2D6 (e.g. quinidine, fluoxetine, or paroxetine). Though these drugs are safe to take with
aripiprazole, they may necessitate dose adjustments to aripiprazole that are slower or smaller
than in the protocol guidelines due to the drugs’ effects on the metabolism of aripiprazole.

XV. DISCONTINUATION OF TREATMENT

There are a number of reasons participants may terminate early from the study. LSIs are
encouraged to discuss potential discontinuations with the Executive Committee, particularly with
respect to potential discontinuations due to protocol deviations as it may be possible to make
accommodations to retain participants who have already been randomized to treatment. Any protocol deviations that are likely to substantially adversely affect the rights, safety, or welfare of the research participant, or the participant’s willingness to continue participation will be reported to the VA CIRB (Form 129). All protocol deviations will be reported to the sponsor regardless of treatment discontinuation decisions.

- **Physician Discretion:** Participants deemed a potential danger to self or others.
- **Participant Worsening:** An increase in depressive symptom severity (e.g., QIDS-C₁₆ > 20% increase for 2 consecutive visits or >40% increase at any visit will trigger a discussion with the study team, including the SI, whether continued participation in the study is warranted. In addition, any participant scoring a 3 on the QIDS-C₁₆ item 12 (suicide ideation) will trigger a more thorough assessment (e.g., administering the Columbia Suicide Ideation Questionnaire) and the individual will be scheduled for weekly visits until there is either improvement in symptoms or study treatment is discontinued.
- **Nonresponse:** Participants who are not improving by Week 8, as measured by the PHQ ≥ 9 or QIDS-C₁₆ ≥ 11 may be considered for early termination due to lack of treatment efficacy.
- **Proscribed Treatment:** Participants who initiate depression-targeted empirically-validated therapy, who initiate a proscribed medication (e.g., changing the index antidepressant or adding quetiapine), or who initiate a proscribed medication dose regimen (e.g., trazodone dose above 100 mg per day) may be exited from the study. Proscribed treatments will be discontinued provided it is in the best interest of the participant. The decision to change or keep a therapy will be discussed with the individual who prescribed the proscribed treatment. The decision to exit a participant due to any of these protocol deviations will be based, in part, on whether or not the initiated treatment was necessary due to study treatment failure.
- **Participant Lost to Follow-Up:** If a participant has missed visits and the Study Coordinator or Independent Evaluator is unable to contact the participant, the participant is considered “Lost to Follow-Up”.


• Noncompliance: If a participant misses more than 2 weeks of study medication the participant cannot continue in the study. If the participant misses two consecutive clinic visits, he/she may be exited from the study.

• Administrative Error: Participants who do not meet all study inclusion or exclusion criteria may enter the study in error. Once this is learned, the participant may need to be exited from the study.

XVI. METHODS TO MAXIMIZE ADHERENCE
Participant adherence is vital to treatment success and to the success of VAST-D. Patient education on study procedures and treatment approaches in VAST-D is the cornerstone of training and adherence monitoring. Moreover, the self-rated measures of depressive symptoms function and side effects will assist patients in disease management. Participant adherence to treatment is increased with patient education. The Study Coordinators will provide patient education initially (as the study aims, procedures, risks, and benefits are detailed in obtaining written informed consent). At study entry, participants will receive the patient pamphlet on depression and a pamphlet describing VAST-D. To maximize retention, Study Coordinators will maintain a substantial focus, especially in the initial meetings with participants, on developing a strong alliance, educating them about depression and the study, preparing them for what to expect clinically, understanding the importance of adhering to treatment, what is expected of them as a study participant, and eliciting a commitment. The importance of working with the clinician and accurately completing the FIBSER to assist in appropriate dose adjustment will also be highlighted. The study coordinator and study physician will emphasize the need to properly adhere to prescribed treatments, even if feeling better, or to call to revise the treatment if side effects occur or therapeutic effects are lost.

XVII. MONITORING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS (SAE)
A. Suicide-Related Risks Monitoring
Despite the occurrence of paradoxical effects during antidepressant pharmacotherapy, it is widely acknowledged that there are more suicide-related risks associated with untreated depression than emerge as a result of antidepressant pharmacotherapy (Simon, Savarino et al.)
In this study, participating patients are exposed to medications they would routinely be prescribed in doses that are routine in clinical practice and for duration of time that mirrors consensually-recommended preferred practices. As such, this protocol is consistent with standard care. Therefore, study-related risks are considered to be no greater than usual clinical care. In fact, because of the use of flexible dosing procedures, measurement-based treatment guidelines, frequent visits and close monitoring, it may be argued that the risks are less than for treatment as usual. Nevertheless, suicide risk should always be acknowledged in the treatment of patients with MDD, ideation must always be taken seriously and patients with MDD should always be monitored for increases in risk.

In VAST-D suicide risk will be considerably mitigated by the systematic and careful assessment of suicidality throughout the protocol. The following risk assessment procedures will be utilized: Participants will be assessed at baseline using a structured clinical interview for current and lifetime suicide risk, the Columbia Suicide Severity Risk Scale (C-SSRS). This instrument provides information about past history of suicidal ideation and attempts as well as information about recent and current suicidal thinking, plans and attempts. There are subscales pertaining to reckless or neglectful behavior and assessing reasons for living. The C-SSRS will be administered by the study team members who complete and maintain active C-SSRS certification training (e.g., Study Coordinators or Independent Evaluators) and information obtained from this assessment will be provided to the study clinician. Participants with a past history of attempt(s) and/or current serious ideation will be flagged for the clinician and SI.

Additionally, at each visit, depression symptoms will be monitored, with the risk for suicide thoroughly assessed. The QIDS-C\textsubscript{16} is administered by the Independent Evaluator at each visit. He/she will notify the study physician whenever there is an increase in the score of item 12 (suicidal ideation) so that a more detailed clinical assessment can be completed. Any participant scoring a 3 on the QIDS-C\textsubscript{16} item 12 will trigger a more thorough assessment (e.g., administering the Columbia Suicide Ideation Questionnaire). Depending upon assessed risk, treating physicians will follow the safety procedures outlined in Table 8 below. Minimally, the individual will be scheduled for weekly visits until there is either improvement in symptoms or study treatment is discontinued.
Table 8. Guidelines for Clinical Action Plans Depending on Level of Risk

<table>
<thead>
<tr>
<th>LEVEL OF SUICIDE RISK</th>
<th>CLINICIAN ACTION PLAN</th>
<th>DOCUMENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Nothing</td>
<td>No suicidal ideation, plan, intent, or attempt; No psychotic symptoms. No high-risk behaviors.</td>
</tr>
<tr>
<td>Low Risk: Participant feels he/she would be better off dead; passive SI.</td>
<td>Make sure the patient does not have suicide plan and/or suicide intent. Obtain agreement to contact the clinician and/or to Psychiatric Emergency Clinic (PEC) during work hours or to the ER after 4pm or week-ends if the suicidal ideation worsens.</td>
<td>Content of passive suicidal ideation as well as no intent, no plan. Patient agreement to contact clinician; Steps to take if suicide risk increases.</td>
</tr>
<tr>
<td>Some Risk: Active suicidal ideation or desire to harm self, has thoughts about how to do this, but not currently intending to carry it out.</td>
<td>Confirm that there is no current intent to act on suicidal plans. If the suicide plan, or desire to harm self, is seriously considered, follow the directions below (Intermediate risk). If the patient clearly states that he or she would never act on this plan, ask for the reasons, develop a safety plan including steps to be taken if the suicidal ideation increases in severity, and obtain agreement; document the conversation.</td>
<td>Identify the plan or how the patient has thought of completing suicide Estimated level of risk, including reasons for living; Detailed description of any safety plan including patient agreement, or reason why this was not considered necessary. Steps to take if suicide risk increases.</td>
</tr>
<tr>
<td>Definite Risk: Seriously considered plan, or very strong desire to harm self</td>
<td>Study physician review in detail suicide plan, including details of where, when and how the patient would carry this out and assess level of intent. Verify reasons for living and ensure that these currently outweigh reasons for dying and/or that the patient is not intending to carry out a plan to harm her/himself in the immediate future. Discuss triggers for suicidal thinking and develop a management plan. If significant other is included in plan, call or speak directly to this person and obtain agreement for management plan. Notify project coordinator and SI of the occurrence of intermediate risk suicidal ideation. If any doubt about safety, escort participant to PC or hospitalize.</td>
<td>Suicide plan, intent and reasons for living. Safety plan, including patient agreement, and agreement of significant other, if included in the plan; If applicable, reason(s) why sending the patient to the PEC or ER was deemed not necessary; Plan for follow up, including Steps to take if risk increases.</td>
</tr>
<tr>
<td>High/Urgent Risk: immediate intent to harm self</td>
<td>The patient is escorted to the PEC or ER or another appropriate safety plan is implemented. If the participant is not in the clinic (phone contact) ask to talk to a relative who might accompany pt. to ER. If necessary call police, to initiate transport and admission to the ER. Contact ER as soon as patient is referred there and transfer necessary assessment information. Notify the SI immediately.</td>
<td>Details of assessment of suicidality and safety plan. Reason for referral to the PEC or ER; plan for follow up, including contact with ER physician, significant other; plan for termination from study and post-study clinical management</td>
</tr>
</tbody>
</table>

All data forms completed by the participant will be reviewed for content by the Study Coordinators before the patient leaves the clinic. This will ensure that nothing is overlooked in the evaluation process, including any indication of new or increased suicidal thoughts or behaviors.
In addition to the procedures, on-going follow-up and systematic evaluation documented above, Study Physician, Study Coordinator and SI contact numbers are provided, and patients are encouraged to call should they need additional assistance beyond scheduled appointments. The study physicians and Study Coordinators will maintain close contact with participants and reschedule appointments as needed. Either the participant or the physician may discontinue the patient’s study participation at any time should the patient’s symptoms worsen or if the patient simply desires to withdraw. When necessary, hospitalization will be available.

Additionally, the 24-hour telephone coverage through a national VA suicide hotline also will be available to patients to minimize the risk of suicide. Veterans will be provided information on the VA Veterans' Crisis Line 1-800-273-TALK (8255), which is available around-the-clock, seven days a week and the National Suicide Prevention Lifeline website. Veterans (and family members or friends) can access Veterans Chat through the National Suicide Prevention Lifeline website. Veterans Chat enables Veterans, their families and friends to go online where they can anonymously chat with a trained VA counselor. If the chats are determined to be a crisis, the counselor can take immediate steps to transfer the chatter to the VA Suicide Prevention Hotline, where further counseling and referral services are provided and crisis intervention steps can be taken. Each VA Medical Center has a suicide prevention coordinator to make sure Veterans receive needed counseling and services. Calls from the Lifeline are referred to those coordinators. Veterans will also be provided information on how to locate the suicide coordinator in his/her area.

At each visit, the patient will complete a self-report (the FIBSER) form indicating any frequency, severity and overall burden of side effects to the study treatment. In addition, the clinician will complete a side effect rating at each visit. Because one of the treatments involves the use of a SGA, movement disorder scales (the Barnes Akathisia Scale) also will be obtained at baseline and weeks 12, 24, and 36. All information will be used by the study physician, along with any other pertinent medical information the patient reports. Depression symptoms will be monitored at each visit, with the risk for suicide thoroughly assessed. All data forms completed by the patient will be reviewed for content by the Study Coordinator or Independent Evaluator before
the patient leaves the clinic. This will ensure that nothing is overlooked in the evaluation process, including any indication of new or increased suicidal thoughts or behaviors. All data collected at each visit are reviewed by the Study Coordinator and study physician so that monitoring of study data for any risk consistently occurs in real time throughout the study.

B. Role of the Local Site Investigator in Adverse Event Monitoring

The local site investigator, as well as other site personnel, shall be personally responsible for the following requirements:

1. Closely monitoring all study subjects for new AEs and/or Serious AEs;
2. Reviewing the accuracy and completeness of all AEs and/or Serious AEs reports;
3. Complying with Cooperative Studies Program (CSP) policies for reporting AEs and/or Serious AEs;
4. Knowing and complying with the VA Central IRB (accessible at http://www.research.va.gov/vacentralirb/) and VHA Handbook 1058.01 Research Reporting Compliance Requirements section 7.a, 7.b and 7.c (accessible at http://www1.va.gov/vhapublications/ViewPublication.asp?pub_ID=2463) reporting requirements for unanticipated problems. Education on the responsibility of site study staff at each participating site to know and comply with these requirements will be a component of the study kickoff meeting, reinforced at study annual meetings, and on periodic conference calls. Questions about managing or reporting of adverse events or serious adverse events will be addressed by the Study Pharmacist at the CSPCRPCC or the CSP #576 National Study Coordinator. These requirements, however, do not eliminate the need for investigators to report both AEs and SAEs to the CSP #576 Sponsor as per the study’s Operations Manual, and;
5. Complying with local Research & Development Committee (R&DC) policies for reporting AEs and/or Serious AEs; and
6. Notifying the VA Central IRB and local R&DC of safety issues reported to the investigator by the Study Sponsor (CSP).

C. Definitions

For CSP 576, AE and SAEs will be collected using the ICH for Clinical Safety Data Management (ICH-E2A) and CSP Global SOP 3.6 definitions as follow:
Adverse Events: An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmacological product which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study intervention.

Serious Adverse Events (SAEs): SAEs are a subset of adverse events. SAE collected for CSP #576 are those defined by the ICH for Clinical Safety Data Management and CSP Global SOP 3.6, as untoward medical occurrence that at any dose:
- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly/birth defect; or
- Any other condition that, based upon medical judgment, may jeopardize the subject and require medical or surgical treatment to prevent one of the above outcomes.

Relatedness: Relatedness involves an assessment of the degree of causality (attributability) between the study intervention and the event. Site investigators will be asked to provide an assessment of relatedness. The assessment provided by the site investigator is part of the information used by the sponsor (CSP) to determine if the AE/SAE represents an alteration in the safety profile of the study intervention. All AE/SAEs with a reasonable causal relationship to the investigative treatment should be considered “related”. A definite relationship does not need to be established.

D. Adverse Events and Serious Adverse Events to be Documented

Adverse Events: All the medications to be utilized in CSP #576 are regularly prescribed in clinical practice for treatment of depression and will be used as indicated in the Official US Prescribing Information (same doses and patient population), and/or as outlined in the VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder-2009 (accessible at http://www.healthquality.va.gov/Major_Depressive_Disorder_MDD_Clinical_Practice_
Guideline.asp). In addition these agents have well characterized adverse effect profiles and there is no reason to expect that treatment with any of these agents as used in CSP #576 will demonstrate a fundamentally different adverse event profiles from the one already known. Therefore for CSP #576 only adverse events considered at least possibly related to the treatment intervention will be documented except as noted below for Serious Adverse Events. To facilitate this documentation, tools designed to detect events related to the agents to be prescribed in CSP #576 will be used: Barnes Akathisia Scale; Frequency, Intensity, and Burden of Side Effects Rating (FIBSER); Arizona Sexual Experience Scale (ASES); Cumulative Illness Rating Scale (CIRS) and a Side Effect Checklist based on the Systematic Assessment for Treatment Emergent Events (SAFTEE). All reportable AEs will be recorded on an Adverse Event Form with an assessment of severity, seriousness, pattern, relatedness and action taken.

**Serious Adverse Events (SAEs):** All SAEs, whether related or not related to the treatment intervention, will be collected for CSP #576. Any SAEs with a reasonable causal relationship to the investigative treatment will be considered “possibly related” or “related”. A definite relationship does not need to be established. All SAEs will be recorded on a Serious Adverse Event Form.

**E. Adverse Event and Serious Adverse Event Monitoring**

For CSP #576, patients will be monitored at each clinic visit and telephone contact for AEs and SAEs. All AEs and SAEs will be recorded on the appropriate event form(s). Active and passive monitoring of AEs and SAEs will begin when a study participant signs the Informed Consent and will continue to the End of Study participation for each study subjects. Additionally investigators will continue to passively monitor subjects and report any SAEs brought to their attention during the 30-day post-study period. Tracking of unresolved SAEs ceases 30 days after the patient completes the study or withdraws consent to be followed.

**F. Expedited Reporting of Serious Adverse Events to CSP**

All SAEs will be promptly reported by submission of the event into the CSP #576 electronic Data Capture (EDC) system within 72 hours of the site investigator being made aware of the event. Email notification of the submission will immediately be relayed by the CSP #576 EDC system to the CSP #576 Biostatistician, Clinical Research Pharmacist, and Study Chairs. The
CSP #576 Clinical Research Pharmacist will be responsible for evaluating all SAEs for immediate patient safety concerns.

G. Reporting of Serious Related and Unexpected Events

For CSP #576, the determination of the expectedness of an event is reserved solely to the study Sponsor – the Cooperative Studies Program. The source of information that will be utilized in the determination of expectedness will include the CSP #576 Drug Information Report, the CSP #576 Informed Consent, the published literature, and the FDA Adverse Event Reporting System (AERS). SAEs that are found by the Sponsor (CSP) to be both related to the investigative treatment and unexpected will be reported to the VA Chief Research and Development Officer, the FDA, and site investigators after review by the Study Chairs, the CSPCRPCC Director and the West Haven CSPCC Director.

H. Reporting of Adverse and Serious Adverse Events to the DMC

The CSP #576 Biostatistician and Clinical Research Pharmacist will tabulate and summarize all AEs and SAEs for the DMC on a schedule set by the DMC. The DMC will also determine when the committee should be unblinded to treatment assignment in reviewing AE/SAE data. The DMC will advise the CSP Director about whether the study should continue or be stopped for safety reasons. The DMC will also monitor the primary endpoint at predetermined intervals and recommend to the West Haven CSPCC Director whether the trial should be stopped for efficacy or futility.

I. Reporting Requirements of the VA Central IRB

Sites are additionally responsible for following the VA Central IRB policy in submitting safety data and protocol deviations. The VA Central IRBs’ most recent policy including a Table of Reporting Requirements, instructions, and forms can be found at http://www.research.va.gov/programs/pride/cirb/policies.cfm.
XVIII. COST EFFECTIVENESS

A. Overview and Perspective
Although ARI might offer some benefits for patients with refractory depression, it is expensive and associated with severe side effects such as weight gain, metabolic disorders, akathisia, headache, and fatigue (Marcus, McQuade et al. 2008; van Winkel, De Hert et al. 2008). The use of ARI may lead patients to obtain additional health care to treat the side effects or lead to non-adherence, resulting in depression relapse and higher medical care costs. BUP-SR is less expensive than ARI: the VA cost of a monthly supply of BUP-SR is $27.56 in contrast to $173.07 for ARI. Moreover, because of its mild side effect profile and its effectiveness at remission, augmentation with BUP-SR may prove to be a more cost-effective strategy than ARI in depression.

We will compare the costs of care under the three treatment regimens and determine the cost-effectiveness of the two augmentation strategies to determine whether one therapy is more cost-effective than the other and whether either augmentation strategy is more cost-effective than monotherapy. We will also compare patient outcomes related to employment and social adjustment by treatment.

A societal viewpoint will be adopted for the main analyses. We will include health care costs (inpatient, outpatient, and pharmacy costs) and travel costs. VA health care costs will be based on the Decision Support System (DSS). Non-VA utilization will be assessed by self report, and we will use unit costs to estimate costs from the utilization. We do not expect there to be time spent by informal caregivers. The cost-effectiveness analysis will use the patients’ lifespan as the time horizon. Outcomes will be expressed in quality-adjusted life years (QALYs). QALYs will be measured at randomization, week 12, at 24 weeks, and at the end of the 36 week follow-up period with the EuroQoL (EQ-5D), which has been used by other researchers to measure significant differences in depression changes (Revicki, Simon et al. 1998; Sapin, Fantino et al. 2004; Peveler, Kendrick et al. 2005; Sobocki, Ekman et al. 2007). We will conduct sensitivity analyses from the perspective of the VA using only VA costs.
B. Costs and Other Economic Measures

B.1. Service Costs:
Health care costs will be obtained from the VA DSS National Data Extracts (NDEs). DSS is an activity-based cost allocation system used in the VA since 1998 and tracks costs for all inpatient stays, outpatient encounters, and pharmacy utilization. Cost data can be linked easily to the VA utilization databases. HERC researchers analyzed the completeness of utilization and cost encounter records that could be merged and found few records that could not be linked (King, Phibbs et al. 2007).

B.2. Service Utilization:
VA health service data will also be obtained from the VA Patient Treatment File (PTF) for inpatient care and the National Patient Care Databases (NPCD) for outpatient care. We will obtain records for all forms of VA care including inpatient hospitalization, nursing home stays, domiciliary stays, standard outpatient visits, and emergency care.

B.3. Non-VA Utilization and Costs:
At baseline, randomization, week 12, week 24, and at the 36 week final assessment, we will survey patients and ask them about any non-VA inpatient, outpatient, and pharmacy utilization occurring during the study period. For inpatient care, we will collect dates and the name of the hospital so that we can avoid duplication (where a person reports the same hospitalization at two follow-up visits). The dates and names will also serve as memory probes (Bhandari and Wagner 2006).

We will estimate the costs of non-VA care by obtaining the costs of different types of VA care (inpatient, outpatient, and pharmacy) from the study sample in DSS records. Using the distribution of these costs, we will assign costs to non-VA care using multiple imputation methods for each type of care.

B.4. Medication Costs:
Antipsychotic and antidepressant drug costs will be measured for the precise doses prescribed during each month. Drug costs will be estimated in a sensitivity analysis using both average wholesale prices (i.e. community costs) (PDR 2009) (Drug Topics Red Book, 2009) and
discounted VA pharmacy costs. The average wholesale price (AWP) of a 30-day supply of ARI was $457.50 compared to $213.19 for BUP-SR. (2009) (PDR 2009) (Drug Topics Red Book, 2009). Insurers and other payers pay less than the AWP (Gencarelli 2005; Gencarelli 2005)); the Medicaid program pays the AWP less 5-16% plus a dispensing fee. We will use 85% of the AWP of drugs plus a $5 per prescription dispensing fee to estimate drug costs. As of 2009, the VA cost of a 30-day supply of ARI was estimated to be approximately $173.07 daily for a 5 mg dose and the cost of BUP-SR was $27.56 for a 150 mg dose.

B.5. Quality-adjusted Life Years (QALYs):
To allow calculation of incremental cost-effectiveness ratios, it important to estimate health status in term of Quality Adjusted Life Years (QALYs), the unit of measurement recommended by the U.S. Public Health Service as the preferred outcome in cost-effectiveness studies (Gold, Siegel et al. 1996). We will use the EuroQoL (EQ-5D) as the measure of patients’ utility levels, which reflect health-related quality of life (1990). The EQ-5D is a self-administered survey with two components: one is a descriptive system that captures different health states by scoring items in five domains of health, placing the combined score in one of 243 possible health states. Each item assesses a different health domain, including mobility, self-care, usual activity, pain/discomfort, or anxiety/depression. The health states are converted to a single index value using population-based preference weights. Preference weights from a U.S. population sample are now available. The second component is a vertical 20 cm visual analogue scale (VAS) that is labeled best health state at the top and worst state at the bottom and is a person’s own assessment of health status.

B.6. Patient Costs:
Since we will adopt a societal perspective for the cost-effectiveness analysis, we must account for costs borne by patients. These costs include the cost of accessing medical care such as travel expenses. We will calculate travel distance for all participants by using distance from a patient’s zip code as recorded in VA utilization datasets to the nearest VA provider. Travel expenses will be estimated as the product of distance traveled and the per-mile travel expense for private automobiles (Phibbs and Luft 1995). We will use the rate allowed as a tax-deduction by the U.S. Internal Revenue Service.
We will also estimate the time spent in obtaining health care, using a count of visits and days of hospital stay. For employed persons patient time will be valued using their wage rates, based on the finding that wage rates are reasonable approximations of opportunity costs (Keeler 2001). For unemployed persons, we will use mean national wage rates by educational attainment, adjusted by age and gender. For retirees, unemployed, and disabled, we will select an appropriate measure of the value of time to reflect their average opportunity cost; usually we assume the time value is minimum wage, and then we adjust for this in the sensitivity analysis.

We will collect self-reported data about the person’s employment status, wages earned, and work and social adjustment periodically through the trial. The following measures assess these domains: an income and employment questionnaire, the Work Productivity and Activity Impairment scale (WPAI), (Mundt, Marks et al. 2002), a 6-item self-report, measures total work hours missed, hours missed due to depression, loss of work productivity because of depression while at work and impact of disease on regular (non-employment) related work activities. Scores are sensitive to depressive symptom change. The Work and Social Adjustment Scale (WSAS) (Reilly, Zbrozek et al. 1993), a 5-item self-report scale, assesses the patient’s view of ability to work, to manage affairs at home and socially, and to form and maintain close relationships. The WSAS was included because of low subject burden (2 minutes), sensitivity to change with treatment, and the importance of this important domain, which is not covered by other measures. All costs and benefits will be discounted using the standard 3% rate.

C. Cost-Effectiveness Analysis
To determine whether a new treatment is cost-effective relative to another treatment, we can express the tradeoffs using the incremental cost-effectiveness ratio (ICER), or the ratio of the extra costs to the extra benefits. If the ICER is below the willingness to pay threshold, then we recommend adoption of the new treatment. The ICER can be estimated directly from the study data:

\[
\text{ICER} = \frac{C_2 - C_1}{E_2 - E_1}
\]

C=cost, E=effect, where drug A is cost-effective relative to drug B if the ICER is below the willingness to pay threshold.
We will use the net benefit regression approach as described by Hoch (Hoch 2009) to determine the cost-effectiveness of ARI and BUP-SR augmentation. The net benefit from treatment is calculated with the following equation where the willingness to pay (WTP) is a predetermined amount that specifies the maximum the VA is willing to spend to improve health. We will measure costs and effect (QALYs) from individual patients as described earlier and calculate each patient’s net benefit (NB) using different values of WTP.

\[ \text{NB}_{i} = \text{WTP} \times \text{Effect}_{i} - \text{Cost}_{i} \]

WTP = $0, $20,000, $50,000
Effect=QALY
Cost=total costs

After obtaining the net benefit for each patient, we will estimate the following regression model:

\[ \text{NB}_{i} = \beta_{0} + \beta_{1} \text{B} + \beta_{2} \text{C} + \text{X} + \epsilon_{i} \]

B=1 if augmentation with BUP, 0 otherwise
C=1 if augmentation with ARI, 0 otherwise
X=vector of patient characteristics

\( \beta_{0} = \) average net benefit (NB) of BUP monotherapy
\( \beta_{1} = \) incremental net benefit (INB) of augmentation with BUP over BUP monotherapy
\( \beta_{2} = \) incremental net benefit (INB) of augmentation with ARI over BUP monotherapy

The interpretation of the estimates obtained from the regression is as follows: if the estimated incremental net benefit is positive for a WTP of $50,000, then the drug will be cost-effective if decision-makers value an extra year of life more than $50,000. We will run a base model with no case-mix adjustment to obtain the INB of the augmentation drugs. We will then include several case-mix characteristics to adjust for any baseline differences between treatment groups. We can include uncertainty by creating a 95% confidence interval for the INB directly from the regression coefficient estimates. We will also run the regression using BUP augmentation as the reference group so that we can obtain the INB of ARI augmentation over BUP augmentation.
We will present cost-effectiveness ratios for both 6-month and lifetime horizons. Morbidity, mortality, and health care utilization beyond 6 months will be calculated on the basis of published studies of people with major depression. A simple Markov chain model will be used to estimate lifetime costs based on study data and on published studies of health care costs for people with depression.

To account for missing economic data and drop out of patients during the trial, we will impute missing values using multiple imputation methods which take into account baseline patient characteristics to impute economic outcomes of similar patients. We will use methods consistent with imputation of other patient data in the trial.

D. Analysis of Other Economic Outcomes

While QALYs were designed to capture differences in quality of life that may be affected by productivity and social adjustment, we will conduct additional analyses looking at specific economic outcomes to determine the impact of improvement in depression on hours worked and participation in social activities. We will compare employment, lost productivity, and social adjustment of participants by treatment group over the study period. We will estimate the change in employment status, hours worked, and social adjustment of patients from baseline to the end of the follow-up period across the different drug treatment strategies. We will run multivariate analyses adjusting for other patient characteristics including age and comorbidity.

E. Inflation and Discounting

Dollar amounts in the study will be presented in terms of currency from a single year, the last year of data collection. We will adjust costs for inflation using the Consumer Price Index for all urban consumers and all goods, the most common measure of nationwide inflation. Because money spent later is less valuable than money spent today, we will also discount expenditures at a rate of 3% per year.

F. Sensitivity Analysis

Because VA drug prices are significantly discounted compared to community drug prices, we will use the adjusted average wholesale price (AWP) of drugs for the main cost and cost-effectiveness analyses. We will include these drug costs in the estimate of total health care costs.
Using community drug prices will allow these findings to be generalizable to patients receiving depression drugs outside the VA.

We will take the perspective of the VA in sensitivity analyses. Using VA drug costs from DSS, we will estimate drug costs and include these drug costs in estimating total health care costs. We will also exclude all patient costs in order to determine whether the augmentation drugs are cost-effective to monotherapy when limiting costs to only costs incurred by the VA. Using these alternative set of cost estimates, we will compare costs between treatment groups to determine whether there are significant cost differences. We will conduct the cost-effectiveness analyses previously described with these VA cost estimates to determine whether the cost-effectiveness findings differ using only VA costs.

XIX. LIMITATIONS OF THE PROTOCOL

VAST-D, although extensive, cannot answer every question regarding the treatment of MDD after an initial SSRI, SNRI or mirtazapine trial fails to achieve a satisfactory outcome. The strategies selected for study represent rational, evidence-based, theoretically-grounded alternatives and are the most common approaches used in practice, there are other possibilities that could be considered, some FDA approved for depression treatment and some not (e.g., tricyclics, monoamine oxidase inhibitors or other SSRIs/SNRIs) or types (e.g., glutamatergic agents like ketamine, thyroid, or lithium). The evidence in support of these approaches and/or significant concerns regarding safety, tolerability, or patient acceptability are not acceptable for use in a study of this magnitude. Similarly, we are not studying non-medication alternatives, such as rTMS, VNS, exercise, meditation, and other CAM based treatments such as massage, intercessional prayer or herbs such as St. John’s Wort or kava. In VAST-D we will note and document use of some alternative approaches but those that are FDA-approved for MDD (e.g., rTMS or VNS) will be a basis for exclusion from the study. Though we are not evaluating psychotherapy and other psychosocial interventions (e.g. self-help or peer support per se), by building on established VA healthcare guidelines we will be able to measure participation in these activities and use them as covariates in analysis. Despite our use of uniform measurement-based practice guidelines, and regular feedback to clinicians regarding their adherence to these treatment guidelines, we anticipate some variability in the way medications are dosed from site to site and from physician to physician within sites. In
the interest of generalizability of findings and applicability into VA clinical settings, we feel this variability beats the alternative of using strict treatment algorithms or substituting study physicians or Study Coordinator for the actual treating physicians in each clinical site.

XX. QUALITY CONTROL PROCEDURES

A. Standardization/Validation of Measurements

Training for Study Personnel: In order to assure that the symptoms of depression, quality of life, and side effects assessments are collected correctly and consistently among the participating sites, training of study personnel on administering these instruments and procedures will be emphasized at the start-up meeting and throughout the study as outlined below. Dr. Somaia Mohamed, Co-Principal Proponent, will be responsible for overseeing the development and implementation of study clinical and research procedural trainings. WH-CSPCC will be responsible for overseeing the developing and implementing data collection and management training activities.

Start-Up Meeting: A comprehensive 2-day orientation and training will occur prior to initiation of enrollment of patients into the study, after all procedures are finalized and described in the Operations Manual. In addition to the Study Co-Chairs, other members of the Executive Committee, the Lead Evaluator (affiliated with a Study Co-Chair’s Office) and staff from CSP program sites, three representatives from each participating site will be expected to attend: the Site Investigator (SI), the Study Coordinator (SC) and the Independent Evaluator (IE). An initial plenary session to start the meeting will include introductions and a detailed presentation of the rationale, methodology and procedures of the VAST-D research protocol which will be relevant to all study personnel. Specifically, the morning plenary session will cover the study aims and protocol; issues in the protection of human subjects and IRB processes; the organizational structure of the study and role of CSPCC, CSPCRPCC, and VA structure; clinical treatment and research procedures, including fidelity to the protocol and safety procedures; the program management and monitoring system; research procedures including understanding reliability and validity, data collection and transmission and other data integrity procedures; administration of study screening, baseline and outcome assessments; and administrative procedures and problem solving. Also, alliance building and methods of enhancing recruitment, retention, and other study
targets will be included. Finally, support mechanisms will be identified (e.g., who to contact for aid, questions, resources). After the initial morning session, subsequent training will have differential emphases depending upon the group being trained.

**Group Specific Meetings:** SCs and IEs will be provided educational material and interactive training on administering depression symptom questionnaires and on recognizing and clinically diagnosing depression led by Study Chairs and the Lead Evaluator.

**SC Training:** Training for SCs on data management topics will be led by the CSPCC study team and will include training in the use of the web-based communications system, general data entry and management procedures, correcting data, coding missing data, and running reports, as well as other topics. Training for SCs on administration of the baseline and outcome instruments for which they are responsible (e.g., the M.I.N.I., CIRS and BAS), will be led by the Study Chairs and the Lead Evaluator and will include presentations of simulated examinations. SCs, with the assistance of the SIs will be responsible for implementing training for Study Clinicians on site at each VA clinical site utilizing the Clinician and Operations Manuals, and a training outline and materials developed under the direction of the Study Chairs’ Offices and CSPCC.

**IE Training:** IEs will be provided detailed training on administering the QIDS-C16, the study's primary outcome measure. The training will include observing and rating clinical vignettes. This training will be led by the Lead Evaluator, in conjunction with the Study Chairs and members of the Executive Committee. IEs will be required to be 'certified' on the QIDS-C-16. Certification will require diagnostic concordance with "expert" ratings on at least 2 interviews based on 1) no more than 1 point (plus or minus) difference on any individual item of the QIDS-C16 and 2) no more than 3 point difference (plus or minus) on the total score. To prevent "drift" intermittent case vignettes will be presented, scored and discussed during regularly scheduled teleconferences. To monitor reliability, recertification will be required at the Training Update Meeting.

**Site Investigator Training:** SIs will be trained on the study aims and protocol including treatment tactics, pharmacology, side effects, drug interactions, and recommended treatment procedures.
Overview and interpretation of clinical measures, including measures covering symptoms, function, and side effects, and those used to implement and adjust treatments, will be reviewed, as well as risks and benefits to patients for study participation and the reporting of Serious Adverse Events. Simulated case vignettes will be used. Also included will be methods to enhance recruitment, retention, and other study targets. Typical barriers to making effective contributions to the study will be proactively addressed (e.g., concern about impact on physician/patient relationship; concern about time/resources).

**Ongoing Teleconferences and Web-based Live Meetings:** Training updates in clinical and research procedures and special topics will be reviewed on an ongoing basis during scheduled and ad hoc teleconferences. Initially, there will be weekly teleconferences of for SIs and SCs and monthly teleconferences or webinars for IEs. Over time, the weekly teleconferences may be phased down to every other week and eventually every month. These conference calls are meant to reinforce enrollment procedures, and to keep clinical and research methods updated and well communicated. For the IEs, teleconferences are meant to help maintain reliability and prevent rating 'drift'. During all contacts, study leadership elicits issues or concerns arising from the SIs, SCs and IEs and adds or changes procedures to address them. Data addressing performance in areas critical to completing the study, such as recruitment and retention, are also reviewed for identification of additional training needs. Study performance data collected by the CSPCC will be used to continuously update training needs as changes occur or as the program management and monitoring system identifies areas that need additional focus and/or retraining such as fidelity to the protocol or recruitment.

**Training Update Meeting:** Training updates (as well as quality control) are addressed for all groups during all Study Group Meetings and web-based meetings. At Study Group Meetings, SCs and IEs will receive supervision on performing clinical ratings of tapes. The Lead Evaluator will be responsible for overseeing the ongoing training of the IEs.

**B. Protocol Deviations**

Documentation will be required for any protocol deviation or breach of protocol. Protocol deviations will be documented on study case report forms, in memoranda to file and progress notes, and submitted to trial management and the local IRB and VA Central IRB, as appropriate.
Any medical center with repeated protocol violations may be recommended to the DMC for termination. If a participating SI feels that adherence to the protocol will in any way be detrimental to a particular patient’s health or well being, the interest of the patient must take precedence. In addition to SMART visits, WH-CSPCC, the Executive Committee, and DMC will monitor protocol adherence centrally. The Executive Committee will consider recommending a site visit for any participating center with repeated protocol violations.

C. Site Performance Monitoring

Strict adherence to the protocol will be expected of every participating site and will be monitored by the DMC, the Executive Committee, and the Study Group. SMART will conduct at least one site visit to each site during the enrollment period for monitoring GCP and study protocol adherence (see Section XII).

By agreeing to participate in this study, the medical center delegates the responsibility for global monitoring of the ongoing study to the DMC, the Cooperative Studies Evaluation Committee, and the West Haven Cooperative Studies Program Coordinating Center. However, the Research and Development (R&D) Committee and the Human Studies Subcommittee/Institutional Review Board (IRB) at each participating medical center may require the local investigators to submit annual reports concerning the status of the study at the medical center for local monitoring purposes.

Data quality and the completeness of data retrieval will be closely monitored on an ongoing basis by the Coordinating Center. The Study Biostatistician will present interim monitoring reports (overall and by site) to the Executive Committee and DMC that will include the following types of information: recruitment of participants, characteristics of the population, completeness of data retrieval and data quality. If a site is identified as an outlier in terms of data quality, a site conference call or site visit will be initiated to assess the reasons that problems are occurring and how they can be corrected. If the problems continue, the site may be placed on probation or terminated from the study if the problems cannot be corrected.

D. Site Visits

Monitoring of sites participating in this study will be executed according to CSP guidelines. A GCP reviewer from the Monitoring, Auditing and Resource Team (SMART) (See Section XXII) will visit all study centers at least once during the course of the study. The purpose of these
visits is to encourage and assess compliance with Good Clinical Practice requirements. The Site investigator will be contacted prior to the visit to arrange a mutually agreeable time for the visit. The reviewer will be at the site for approximately two days to review study records and discuss the conduct of the trial. Reviewers will examine participant study files, including source documents held electronically, in clinic files and participants’ official medical records and will review regulatory/essential documents, such as IRB correspondence and FDA regulatory documents. Areas of particular concern will be informed consent issues, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, patient records, and site operations/investigator involvement.

Additional monitoring visits may be conducted as deemed necessary by study leadership, CSP program site leadership or SMART. Additional for-cause audits will be conducted when requested by study leadership or CSP Central Office. For-cause audits can be announced or unannounced. Also, the Coordinating Center will monitor study sites remotely through weekly reports, data review and queries, and Study Group conference calls.

E. West Haven Quality Assurance Section
The Quality Assurance Section, West Haven CSPCC will provide central monitoring of study sites to ensure compliance with Good Clinical Practice. Monitoring may include but not be limited to the informed consent process, data validation, source verification, and safety reporting. Additional site-specific monitoring may be conducted if triggered by study performance metrics. Site performance findings may result in on-site visits by a CSPCC QA Nurse Specialist or other CSPCC central monitoring personnel to evaluate the need for additional site training to remedy compliance concerns.

F. Probation/Termination of Participating Centers
The Study Chairpersons and the Study Biostatistician will monitor the patient intake rate and operational aspects of the study. Participating medical centers will continue in the study only if adequate patient intake is maintained. The Executive Committee may take action leading to the
discontinuation of patient enrollment at a center only with the concurrence of the DMC and CRADO.

If recruitment is not proceeding at an appropriate rate, the Study Chairpersons and the Study Biostatisticians will scrutinize the reasons for patient exclusions. Based on this information, the Executive Committee may choose, with the approval of the DMC and CRADO, to drop centers or add additional centers, or to make minor modifications to the inclusion/exclusion criteria. Medical centers will only be allowed to continue in the study if adequate patient intake is maintained. The expected recruitment to maintain full funding is 25 patients randomized per site per year. Understanding that there is a ramp-up in recruitment early on, participating sites that do not enroll at least 6 participants during their first three months or 12 participants within six months will be considered for probation or reduction in funding. Centers that fail to randomize at least 4 participants during any 3-month period of the study will be considered for probation and potential reduction in site support. If a medical center is placed on probation, the Study Chairpersons and Study Biostatistician will confer with the site personnel and visit the site, if necessary, to help improve the rate of recruitment. If there is no improvement in accrual after the probation period, the site may be subject to reduced funding or possible termination as a study site. The Executive Committee will only take actions leading to discontinuation of a center with the concurrence of the DMC or the CSP Director. If a center is terminated from the trial, resources will be reallocated to other sites that may be exceeding the recruitment goals or be used to start up a backup site.
XXI. DATA MANAGEMENT

A. Data Collection Methods

A.1. Electronic Data Capture (EDC)

The data for CSP#576 will be managed by the WH-CSPCC using a web-based Electronic Data Capture (EDC) system that is based in Microsoft InfoPath form and hosted in Microsoft SharePoint on a secure VA server located in a regional VA data center. This system allows approved site investigators and personnel to enter study patient data directly into web-based forms and thus track and manage their patients, complete randomization, record data in electronic case report forms (CRF), obtain study medication kit assignments, receive data clarifications and correct patient data online. Data collected on source documents at the site (paper and/or electronic medical records) will be entered in the EDC system and be submitted to a central study database. Paper versions of the CRF will be supplied to the sites for recording of source clinical data and for patients to record self-reported responses to mental health and general quality of life questionnaires. At this time, accessing the system requires connection to the VA intranet connection. Users must have a valid VA username (controlled by VA OIT) and must have a separate permission to access the SharePoint site (controlled by the WH-CSPCC SharePoint Administrator).

EDC application designers at WH-CSPCC will create a study-specific database definition that includes electronic case report forms, a randomization and study medication kit assignment menu and data query/clarification process. Data clarifications (DCF) or data queries will be managed in two ways. Certain queries will be programmed into the forms that are designed to activate upon data entry and provide cleaning of the data before it is submitted to the database. Additional DCFs will be entered into the EDC system manually during data review or programmed to perform systematic cross-form checks using tools within the EDC system. Backend data checking will also be performed using such tools as SAS programming. Any DCFs generated on the backend will be either uploaded into the EDC system or, if that is not possible, distributed to the sites by tracked mail or electronically for processing. DCFs for a data field or form can be entered into the EDC system by site personnel, CSPCC or CSPCRPCC...
personnel, or by approved site monitoring personnel (e.g., VA SMART) as will be prescribed in the study Operations Manual.

Updates to the electronic forms and database can be generated during the study without impacting collected data. Study reports will be generated from exported data in order to track the study progress and to monitor adverse events, in particular Serious Adverse Events. Study reports will be circulated to appropriate members, including the Study Chairpersons, the Site Investigators, CSP program sites, the Executive Committee, and the Data Monitoring Committee.

A.2. Paper CRF and Source Document Tools

Although EDC will be used to collect study data for the study central database, paper data collection tools will still be needed at the sites. Any information that is not recorded in the study patient’s VA electronic medical record will need to be recorded on a source document tool or paper study CRF. Paper CRF will be required for two reasons: 1) Collection of patient self-reported responses to study questionnaires, and 2) as a backup in the event that the EDC system is not accessible due to system/network failure or downtime. The paper CRF will be readable by optical character recognition software (e.g. Teleform ® Elite v. 9.0, by Cardiff, Inc.). Electronic scanner-readable e-PDF versions of the data collection forms will be sent to the sites. The e-PDF versions may be completed on a personal computer at the study site. If a form is completed on a personal computer or terminal, a completed copy of the form must be printed. The printed copy will be faxed to the WH-CSPCC fax data server. The printed copy kept at the site will be filed in the patient study folder. Once the forms are received at WH-CSPCC, the will be processed through the Teleform form reader and verifier software where a research assistant at the WH-CSPCC will review the forms for consistency and completeness. Forms that have major deficiencies or are not accepted by the reader will be reconciled with the site personnel by telephone calls or e-mails, usually by requesting a resubmission of the completed form with corrections annotated. CRF processed by the Teleform Verifier will exported as an image file folder and the extracted data items will be exported to a comma-delimited file in a data capture folder, both on a secure WH-CSPCC file server. Data captured in this way will be uploaded into the central study database. All changes or corrections to data entered on paper CRF forms will
be dated and initialed by site personnel making the change on the original CRF and on the associated data edit sheet, if applicable.

**B. Data Quality Control**

After the study is approved, the Case Report Forms (CRFs) will be field-tested using the EDC system. Communication between WH-CSPCC, CSPCRPCC, the Study Sites and the central database will be tested.

The EDC system will manage data clarifications or data queries in two ways. Some queries will be programmed into the forms and the site personnel completing the form will be notified immediately if an entered value is out of range.

On at least a weekly basis, programmers at WH-CSPCC will transfer the cumulative data in the central MS SQL database to SAS datasets on the CSPCC UNIX server. SAS programs will be run to generate reports that summarize the accumulated study data and data exceptions (e.g., missing forms or data, and any out of range values). For any DCF that cannot be generated in the EDC system, computer-generated notices will be distributed directly to the site personnel to address. These notices may request completion, correction, or verification of specific data items. A computerized record will be kept of the number and types of errors to ensure a high level of data integrity. Interim progress reports of cumulative errors and overall data quality of the EDC system will be sent to the investigators, the Executive Committee, and the DMC. Unresolved data queries will be included in the datasets that will be used in interim reports. However, every effort will be made to resolve all outstanding DCF prior to a DMC report.

Data files on the central study database containing the accumulated patient information will be examined for completeness and consistency at regular intervals. Tested and validated computer programs will check newly entered forms for missing or out-of-range values. Computer-generated notices will be mailed to the participating investigators requesting completion for forms and follow-up on DCF for correction or verification of specific data items. A summary of the computer-generated edit messages indicating the questionable (e.g., out-of-range or missing values) data will be used to monitor coding errors and to edit the data on the main computer file.
when the requested information is returned. A computerized record of the types of errors will be kept in order to ensure a high level of data integrity.

At periodic intervals, a cumulative record of errors and data quality progress reports will be sent to investigators and the Study Chairmen. Data edits and removal of duplicate records will be applied to the data files on a regular basis, and cleaned (final) files through the time of the most recent running of data edits will be created. These final files will be used to run monitoring reports on a regular basis. The progress of data collection will be monitored with computerized data form inventory programs that will produce a profile of all forms expected and received for each study patient. Missing-forms reports will be generated and sent to the sites periodically during the enrollment phase of the study.

Data quality will be monitored on an ongoing basis by the WH-CSPCC. The Study Biostatistician will present interim monitoring reports to the Executive Committee at least monthly and to the DMC at least annually. Interim reports will include recruitment of participants, characteristics of the population, completeness of data retrieval, and data quality. Prototype tables are given in the Appendix and serve as an example of the statistical reports that will be generated for study monitoring by the Executive Committee and the DMC.

C. Electronic Study File

CSP has established a Clinical Trials Management System is hosted on a server at a secure VA regional data facility is based in a MS SharePoint platform. An MS SharePoint site will be used for maintaining an electronic version of the Central Study File for this study. Most of the operational aspects of the study will be managed using this SharePoint web site. Participating medical centers will be able to access current and past versions of the Study Protocol, Operations Manual, operation memorandum and other work instructions, CRFs, and other study related documentation, as well as meeting announcements, conference call notices, and study newsletters. This website will also provide a portal to the EDC system for study personnel with appropriate approvals.
D. Quality Control of the Process

After the study is approved, the Study Chairmen and the WH-CSPCC will prepare an Operations Manual that will be provided to the investigators as a guide to the operation and management of the study as well as a technical reference manual. A training session will be held at the study kick-off meeting for all study personnel in order to: (1) assure uniformity in patient management and data collection procedures, and (2) train the personnel in study procedures and criteria.

Study procedures will be reinforced by the use of regular conference calls, particularly in the first few months of the study and by the periodic distribution of a study newsletter. All study personnel will attend group meetings during the enrollment period when study procedures again will be discussed in detail. The Study Chairmen’s Office and the WH-CSPCC study personnel will be available to clarify study procedures by telephone, fax and e-mail.

If the Executive Committee determines that a procedure must be changed, the participating sites will be informed by conference call and/or newsletter and an updated section of the Operations Manual pertinent to the changed procedure will be provided to all sites.

The trial will be conducted in compliance with Good Clinical Practices (see Section XV).

E. Data Security

CSP has a commitment to maintaining data security and patient privacy. Standard practices and policies as part of the responsible conduct of clinical research studies are implemented and reviewed periodically. CSP Center Directors are responsible for ensuring that all CSP Data Security Policies are enforced within their Centers. All study data collected will be handled, maintained and stored according to CSP standard practices and policies. This includes:

1. Protected Health Information (PHI) as defined by HIPAA will not be used for any purpose that is not related to the activities of this study.
2. Records are identified only by a patient identification number.
   a. Patient identification numbers are not derived from or related to information about an individual.
b. All electronic PHI are stored on secure servers and may not be moved to a PC or other external device.

c. Paper CRFs, if any, are stored in locked file cabinets and rooms.

3. When necessary, PHI (exclusive of HCPHI) may be transported between secure servers. PHI must be encrypted and password protected while being transferred using a FIPS 140-2 certified program. Any removable storage device used to transfer PHI (e.g., hard-copy printouts, data tapes, encrypted CDs, encrypted USB drives, etc.) should either be destroyed after transfer is complete or given to the Data Security Administrator to be secured in a secure, fireproof safe. A trackable mail system must be used for the physical data transfers.

4. Data from studies are utilized at CSPCC and are not removed from the Center.

5. E-mail is not permitted to transmit PHI unless approved by the Center Director. No PHI may be sent via MS Outlook or Exchange unless the message is secured utilizing encryption and VA authorized security protocol.

6. Documents sent for medical evaluation purposes (e.g., endpoint adjudication) are sent via trackable express mail. Personal information is redacted by the VAMC or CSPCC if not determined to be necessary for completing the evaluation.

7. Only VA-owned equipment or equipment configured to VA security standards is permitted to connect to the CSP networks in accordance with VA Directive 6504.

8. Training, reminders, and signed data security statements are used to ensure CSP personnel understand VA policies.

9. Sharing of CSP study data outside of CSP requires the approval of the Director, CSRD and data use agreements. In addition, sharing of data outside of the VA requires local ISO, PO, and ACOS-R approvals.

The EDC system used for data collection in this study was developed by the Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC) in Boston, Massachusetts. Their goal was to develop a MS InfoPath/SharePoint electronic data capture tool that is fully compliant with US Federal regulations regarding electronic web based data capture systems established by the Food and Drug Administration under 21 CFR 11. Data entered directly into the EDC central database provides the official clinical record for data collection. Source documentation is handled in the same manner as a paper based system. All paper-based
records will be kept under lock and key. The MS InfoPath/SharePoint electronic data capture system will be validated by the WH-CSPCC Quality Assurance Team to ensure the integrity of the data capture software.

When the study is ongoing, the electronic data capture system will utilize state-of-the-art technologies in order to protect the data during transmission. All of these technologies exceed the current VA standards for transport. In brief, electronic systems will employ secure socket layer technology and FIPS 140-2 compliant encryption algorithms to ensure that data is not vulnerable during transport. In addition, all data will be stored behind the VA firewall and will be password protected at all times. Hard copy data will be sent via a traceable mail system (i.e., FEDEX), via a courier, or via secure fax.

The servers housing the study databases will be located at a secure VA facility. This facility has yet to be determined (Either a Hines, IL, or Philadelphia, PA, Regional VA Data Facility) but the one chosen will support round the clock web services and monitoring within a secure VA environment in order to provide an optimal infrastructure for the protection of sensitive information. The clinical database with all research data will be housed behind the VA firewall on VA owned and maintained servers. Additionally, the system will be monitored by the WH-CSPCC Quality Assurance and Information Technology teams to ensure that all applicable VA regulations and directives are strictly followed.

Access to the study data housed within the MS InfoPath/SharePoint system will be afforded the same level of security as all forms of VA protected and/or highly sensitive information. Access is heavily restricted to individuals with CSP approval to access the data. Individuals must be properly credentialed research staff and must be compliant with VA security trainings (i.e., Research Data Security, HIPAA and VA Privacy Training, Cyber-Security, and Good Clinical Practices). In addition, research data will be stored on VA secure servers with restricted permissions for copying and exporting data. Only properly approved Coordinating Center personnel will have the ability to copy and export data. These individuals have received training on the local SOP governing their permissions and will not access or export data without written approval from the Coordinating Center Director. Furthermore, the permissions of the electronic
systems are structured such that individual sites can only see the data for their study participants, and they cannot see or access the data for another clinical site or for another participant.

Backup copies of the database will be transferred behind the VA firewall to the WH-CSPCC on a frequent basis depending on the study need. These backup copies will be transferred and stored across secure connections according to VA regulations and WH-CSPCC operating procedures. Periodic off-site back-ups will be made as part of a comprehensive disaster recovery plan. The Director of Information Technology will ensure that backup media are stored in compliance with all federal and VA regulations on the storage of potentially sensitive information. The Director of Information Technology will also ensure that all backup media is encrypted in compliance with the current best practices established and approved by the Center Director. Encrypted backup media will be stored in a physically secure location with access restricted to essential personnel. Access to back-ups may be at the discretion of the Center Director and/or the Director of Information Technology.

XXII. GOOD CLINICAL PRACTICES (GCP)
This trial will be conducted in compliance with Good Clinical Practices. Monitoring of sites participating in the trial will be executed according to the Cooperative Studies Program (CSP) Guidelines. A GCP Reviewer from the Site Monitoring, Auditing and Resource Team (SMART) will visit all VA centers, at least once, during the course of the study. The purpose of these visits is to encourage and assess compliance with Good Clinical Practice requirements. Reviewers will examine patient study files including source documents in both the clinic files and the patients’ official VA medical records and will also review regulatory/essential documents such as correspondence with the IRB and the Sponsor (CSP). Areas of particular concern will be patient informed consent issues, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, patient records, drug accountability and investigator supervision and involvement in the trial. Reports will be prepared following the visit and forwarded to the investigator, the Study Chair and CSPCC Director.

A. Good Clinical Practices and Human Subject’s Protection Training
All site personnel involved with the conduct of this study will be certified in Good Clinical Practices (GCP) and Human Subjects Protection training. GCP training will be conducted at the
organizational (kick-off) meeting. Site personnel will be required to attend this training at the organizational meeting. Site investigators are welcome and are encouraged to attend the training. After GCP and Human Subjects Protection training at the organizational meeting, the general VA research requirement for training in these subjects at least every two years can be obtained by completing approved training, such as the online computer based training offered by VA Office of Research and Development. Written verification of GCP and Human Subjects Protection training of site personnel will be submitted to the West Haven CSPCC prior to the start of patient enrollment at each site. Any site personnel who are hired after the organizational meeting must complete the general training mandated by VA Research prior to working on the trial.

B. Patient Informed Consent

Protection of the rights and welfare of patients is a primary concern of the VA Cooperative Studies Program (Section XI). Informed consent will be documented in this trial by the use of a consent form prepared by each investigator in conjunction with the CSPCC and approved by the VA Central IRB and the investigator site IRB. The prototype consent form provided in the protocol may be adapted to meet local needs (Appendix A.2). This form may be reviewed by the HRC at the CSPCC and contains the basic required elements of informed consent. The consent form, as revised and approved by the local IRB, must be sent to the CSPCC before the trial may begin.

C. GCP Monitoring of Sites

Monitoring of sites participating in this study will be conducted according to CSP guidelines. GCP Reviewers from the CSP Site Monitoring, Auditing and Resource Team (SMART) will visit study sites at study initiation to encourage and assess compliance with GCP requirements. Other GCP site visits to audit performance will be conducted when requested by any of the monitoring bodies. The investigator will be contacted prior to the visit to arrange a mutually agreeable time for the visit. The reviewer will be at the site for approximately two days to review study records and discuss the conduct of the trial. Following the site visit, a summary of findings and observations will be sent to the investigator. The CSPCC HRC will conduct human rights site visits at selected sites during the course of the study. Also the Coordinating Center in
collaboration with SMART will monitor study sites remotely through weekly reports, data queries and site personnel/SI conference calls.

D. Data Security
CSP has a commitment to maintain data security and patient privacy. Standard CSP practices and policies for the conduct of clinical research studies have been implemented and reviewed periodically. CSP Center Directors are responsible for ensuring that all CSP Data Security Policies are enforced within their Centers. CSP employees are responsible for following all CSP Data Security Policies when conducting study work. All study data collected will be handled, maintained and stored at CSPCC according to the CSP standard practices and policies. These include:

Protected Health Information (PHI) as defined by the HIPAA will not be used for any purpose that is not related to the activities of this study.

CSP study data are maintained in secure files at CSPCC and records are identified only by a patient identification number. Patient identification numbers are not derived from or related to information about an individual. All electronic PHI are stored on secure servers and may not be moved to a PC or other external device. Paper CRFs are stored in locked file cabinets and rooms. Highly confidential protected health information (HCPHI: names, SSN, physical and electronic addresses and phone numbers) collected by the study are defined in the informed consent or privacy authorization document, and are stored at the CSPCC separately from other study data. Electronic HCPHI is encrypted and password protected and paper CRFs containing HCPHI are stored in locked filing cabinets and rooms. When necessary, PHI (exclusive of HCPHI) may be transported between secure servers. PHI must be encrypted and password protected while being transferred using a FIPS 140-2 certified program. Any removable storage device used to transfer PHI (e.g., hard-copy printouts, data tapes, CD’s, USB drivers, etc.) should either be destroyed after transfer is complete or given to the Data Security Administrator to be stored in a secure, fireproof safe. A traceable mail system must be used for the physical data transfers.
Data from studies are utilized at CSPCC and are not removed from the Center. E-mail is not permitted to transmit PHI unless approved by the Center Director. No PHI may be sent via MS Outlook or Exchange unless the message is secured utilizing encryption and VA authorized security protocol.

Documents sent for medical evaluation purposes (e.g., endpoint adjudication) are sent via trackable express mail. Personal information is redacted by the VAMC or CSPCC if not determined to be necessary for completing the evaluation.

Only VA-owned equipment or equipment configured to VA security standards is permitted to connect to the CSP networks in accordance with VA Directive 6504. Training, reminders, and signed data security statements are used to ensure CSP personnel understand VA policies.

Sharing of CSP study data outside of CSP requires the approval of the Director, CSRD and data use agreements. In addition, sharing of data outside of VA requires local ISO, PO and ACOS-R approvals.

**E. Archiving Study Records**

At the close of the trial, investigators will be instructed about record retention. No records shall be destroyed without CSP authorization. Research records, including the site investigator’s research records. Must be retained until disposition instructions for research records are approved by the National Archives and Records Administration. The participating site will be encouraged to contact the CSPCC if record storage becomes a problem at the site. The CSPCC will authorize records disposal or discuss an alternative storage location.
XXIII.  BIOSTATISTICAL CONSIDERATIONS

A.  Hypothesized Event Rates and Treatment Effect

Investigations of antidepressant medications and augmentation strategies have used a variety of methods to measure the impact of treatment. The most common methods have included analyses of mean change, mean percent change in scores, and the proportion of patients who reach a threshold for improvement (remission or relative response) on various instruments designed to measure depression symptoms. To meet the objectives of this study, the primary outcome has been chosen to identify recovery from depression in terms of remission rather than changes in scores, which may indicate some improvement in symptoms but does not necessarily translate to recovery from depression. See Section I.C.1 for a more detailed justification for this choice.

The primary outcome of remission of symptoms of major depression will be determined by a threshold response on the Quick Inventory of Depressive Symptomatology – Clinician Rating (QIDS-C16) depression scale of a score 5 or less occurring during the first 12 weeks of follow-up after randomization. This measurement of remission was the primary outcome in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial where 565 patients who had failed on at least one antidepressant were randomized to either sustained-release bupropion (BUP-SR) or buspirone (Trivedi et al., 2006).

The QIDS-C16 score ranges from 0 to 27 where higher scores indicate worsening severity of depression symptoms. A clinician rated measurement has been chosen over self-report so that the primary outcome can be recorded by a blinded evaluator. There is additional discussion of this in the Outcome Measures Section (Section IV).

For sample size estimation, the estimate for remission for patients assigned to bupropion monotherapy was obtained from the STAR*D Study where remission and response were measured using the QIDS-SR (self-report) 16 questionnaire. In that phase of STAR*D, 25.5% of the 239 patients who received bupropion-SR monotherapy for up to 14 weeks after unsuccessful treatment with an SSRI antidepressant achieved remission. Other antidepressant switching regimens achieved 26.6% remission (on sertraline) and 25.0% remission (on extended release
venlafaxine) (Rush et al., NEJM, 2006). In the same study, the Hamilton Rating Scale for Depression (HRSD-17 or HAM-D) yielded a 21.3% remission for bupropion monotherapy. Therefore, in the sample size calculations for CSP #576 a 25.0% conservative estimate of remission will be used for patients assigned to bupropion monotherapy.

Estimates for the treatment effect of an antidepressant medication augmented with bupropion (antidep + BUP-SR) were also obtained from the published results of the STAR*D Study for outcomes after 12 weeks of treatment (Trivedi et al, 2007). In that study, 279 patients were randomized to antidep + BUP-SR and 286 were randomized to buspirone. Remission based on the QIDS-SR16 was 39.0% in the BUP-SR group and 32.9% in the buspirone group. There was no statistically significant difference in remission and response measured by threshold score (a QIDS-SR16 score $\geq 5$) or a threshold relative response (a reduction of $\geq 50\%$ in a patient’s baseline QIDS-SR16 score). However, there was a significant difference in mean percent change in QIDS-SR16 score relative to baseline (-25.3 +/- 43.9 and -17.1 +/- 49.7, p<0.03), and a significant difference in final QIDS-SR16 score (8.0 +/- 5.3 and 9.1 +/- 5.6, p<0.03). In the sample size calculations for CSP#576, 39.0% was used as the highest estimate of remission in the antidep + BUP-SR group, but a more conservative estimate was chosen to be sure the trial is powered adequately to detect a meaningful treatment effect on remission.

A meta-analysis of randomized controlled trials involving patients with depression who received an antidepressant medication augmented with an atypical antipsychotic medication (Nelson and Papakostas, 2009) showed that aripiprazole augmentation significantly reduced symptoms of depression measured by remission at 6 weeks and by mean change in the Montgomery Asberg Depression Rating Score (MADRS) compared to placebo. Two of these studies conducted for the regulatory filing for the indication for augmentation with aripiprazole also recorded remission data at 6 weeks for the HRSD-17; 26.0% remission in the first trial (Berman, 2007) and 25.4% remission in the second trial (Marcus, 2008). A third study 349 patients (177 adjunctive aripiprazole, 172 adjunctive placebo) using the MADRS score for outcomes, reported 36.8% remission at 14 weeks. The different instruments and the different study durations (6 week outcomes for augmentation with aripiprazole vs. 12 week outcomes for bupropion) make it difficult to estimate a QIDS-SR16 score for augmentation with aripiprazole, but the relative
treatment effects combined over the three studies in the meta-analysis provide an estimated odds ratio of 2.09 (95% CI 1.55, 2.81). For the sample size calculation for this study, relative effects at the lower end of the confidence interval (1.55 to 1.76) were used as conservative estimates of treatment effect for augmentation with aripiprazole.

Table 9. Summary of Published Results of Remission and Response for Protocol Monotherapy and Augmentation Strategies.

<table>
<thead>
<tr>
<th>Drug Regimen</th>
<th>Reference</th>
<th>Remission (%)</th>
<th>Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Author</td>
<td>QIDS</td>
<td>HAM-D</td>
</tr>
<tr>
<td>Augmentation with Aripiprazole</td>
<td>Hellerstein</td>
<td>28.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Berman, 2007</td>
<td></td>
<td>26.0</td>
</tr>
<tr>
<td></td>
<td>(6 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marcus, 2008</td>
<td></td>
<td>25.4</td>
</tr>
<tr>
<td></td>
<td>(6 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Berman, 2009</td>
<td></td>
<td>36.8</td>
</tr>
<tr>
<td></td>
<td>(14 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled Atypical Antipsychotic</td>
<td>Nelson, 2009</td>
<td>30.7</td>
<td></td>
</tr>
<tr>
<td>Augmentation with Bupropion</td>
<td>Trivedi, 2007</td>
<td>39.0</td>
<td>29.7</td>
</tr>
<tr>
<td></td>
<td>STAR*D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion Monotherapy</td>
<td>Rush, 2006</td>
<td>25.5</td>
<td>21.3</td>
</tr>
<tr>
<td></td>
<td>STAR*D</td>
<td></td>
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</table>

B. Sample Size and Power

The sample size required for the primary outcome of this study was calculated using the method for the comparison of two proportions where the null hypothesis is that the two proportions are equal (or odds ratio = 1.0). The sample size and power considerations are based on remission occurring in the first 12 weeks after randomization. The following assumptions were used in the determination of sample size and power for the primary hypotheses comparing remission in the two augmentation groups to remission in the bupropion monotherapy group:

1) The primary outcome measure is the binomial proportion of patients achieving protocol-defined remission during the first 12 weeks after randomization.
2) The proportion of patients in remission during the first 12 weeks of treatment among those randomized to the bupropion monotherapy group is estimated to be 25%.

3) The proportion of patients in remission during the first 12 weeks of treatment among those randomized to an antidepressant augmented with aripiprazole is estimated to be 35%, a 10% absolute increase in remission compared to the bupropion monotherapy group (relative odds ratio = 1.62).

4) The proportion of patients in remission during the first 12 weeks of treatment among those randomized to an antidepressant augmented with bupropion is estimated conservatively to be 36%, an 11% relative increase in remission compared to the bupropion monotherapy group (relative odds ratio = 1.69).

5) A two-sided significance level of 0.05 and 90% power is used for the first primary hypothesis test and a two-sided significance level of 0.025 (Hochberg adjustment for multiple comparisons) and 90% power is used for the second primary hypothesis test.

6) Sample size estimates are increased by 15% to account for loss of information due to patients who are lost to follow-up or are withdrawn due to side effects or other reasons not associated with lack of response to treatment in the first 12 weeks. While all patients who discontinue treatment or leave the study due to lack of response to treatment will be counted as treatment failures (non-remission), the sample size is inflated to preserve power against a possible reduction in the effect size due to losses and to protect the power for analyses of secondary outcomes.

7) A minimal loss of Type I error for one interim look at the primary outcome for early efficacy or futility is assumed.

8) The study duration will be 33 months (excluding start-up and closeout periods) with up to 29 months of recruitment and minimum of 36 weeks of follow-up after randomization for those participants randomized in the first 24 months of recruitment. Participants randomized in the last 5 months of the recruitment period (months 25 to 29) and who enter the continuation phase of the study will be censored (i.e., withdrawn from the study prior to completing 36 weeks of follow-up) before the end of the study (i.e., in month 33).
There are two primary hypotheses for comparing each augmentation group separately with the bupropion monotherapy group. The sample size was chosen to maintain at least 90% power for the first primary hypothesis test (hypothesized to be augmentation with aripiprazole vs. monotherapy with bupropion) at the 0.05 significance level, and at least 90% power for the second primary hypothesis test (hypothesized to be augmentation with bupropion vs. monotherapy with bupropion) at the 0.025 level, planning for use of a Hochberg adjustment for multiple comparisons for the co-primary outcomes.

A sample size of 1518 patients (506 per treatment group) will have 90% power to detect a 10% increase in remission in the aripiprazole augmentation group compared to bupropion monotherapy (35% vs. 25% remission, odds ratio = 1.62). For the second hypothesis test, there would be 84% power to detect a 10% increase in remission in the bupropion augmentation group compared to bupropion monotherapy at the 0.025 significance level, and more than 90% power to detect an 11% increase (36% vs. 25% remission, relative odds ratio = 1.69). If remission is actually 39% with bupropion augmentation, as was observed in STAR*D, and 25% for monotherapy (relative odds ratio = 1.92), the study would have nearly 100% power to detect a treatment difference. Different sample size scenarios varying the estimated increase in remission but keeping the expected proportion of patients remitting on monotherapy at 25% on bupropion monotherapy are summarized in Tables 10 and 11 below.

Table 10. Sample Size Estimation Per Group for Varying Remission for an Augmentation Group Relative to 25% Remission at 12 Weeks in the Bupropion Monotherapy Group for 90%, 85%, and 80% Power, \( \alpha = 0.05 \), and adjustment for a 15% Withdrawal Rate

<table>
<thead>
<tr>
<th>Estimate of Remission in Augmentation Group</th>
<th>Increase in Remission Relative to Monotherapy Group</th>
<th>Relative Odds Ratio</th>
<th>95% Power ( \alpha = 0.05 )</th>
<th>90% Power ( \alpha = 0.05 )</th>
<th>85% Power ( \alpha = 0.05 )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sample Size Per Group</td>
<td>Sample Size Per Group</td>
<td>Sample Size Per Group</td>
<td>Sample Size Per Group</td>
<td>Sample Size Per Group</td>
</tr>
<tr>
<td>32%</td>
<td>7%</td>
<td>1.41</td>
<td>1240</td>
<td>1003</td>
<td>858</td>
</tr>
<tr>
<td>33%</td>
<td>8%</td>
<td>1.48</td>
<td>960</td>
<td>777</td>
<td>664</td>
</tr>
<tr>
<td>34%</td>
<td>9%</td>
<td>1.55</td>
<td>765</td>
<td>619</td>
<td>529</td>
</tr>
<tr>
<td><strong>35%</strong></td>
<td><strong>10%</strong></td>
<td><strong>1.62</strong></td>
<td><strong>625</strong></td>
<td><strong>506</strong></td>
<td><strong>433</strong></td>
</tr>
<tr>
<td>36%</td>
<td>11%</td>
<td>1.69</td>
<td>521</td>
<td>423</td>
<td>362</td>
</tr>
<tr>
<td>37%</td>
<td>12%</td>
<td>1.76</td>
<td>442</td>
<td>358</td>
<td>306</td>
</tr>
<tr>
<td>38%</td>
<td>13%</td>
<td>1.84</td>
<td>379</td>
<td>308</td>
<td>263</td>
</tr>
<tr>
<td>39%</td>
<td>14%</td>
<td>1.92</td>
<td>329</td>
<td>267</td>
<td>228</td>
</tr>
</tbody>
</table>
Table 11. Sample Size Estimation Per Group for Varying Remission for an Augmentation Group Relative to 25% Remission at 12 Weeks in the Bupropion Monotherapy Group for 90%, 85% and 80% Power, $\alpha=0.025$, and adjustment for a 15% Withdrawal Rate

<table>
<thead>
<tr>
<th>Estimate of Remission in Augmentation Group</th>
<th>Increase in Remission Relative to Monotherapy Group</th>
<th>Relative Odds Ratio</th>
<th>95% Power $\alpha=0.025$</th>
<th>90% Power $\alpha=0.025$</th>
<th>85% Power $\alpha=0.025$</th>
</tr>
</thead>
<tbody>
<tr>
<td>32%</td>
<td>7%</td>
<td>1.41</td>
<td>1441</td>
<td>1186</td>
<td>1026</td>
</tr>
<tr>
<td>33%</td>
<td>8%</td>
<td>1.48</td>
<td>1115</td>
<td>917</td>
<td>794</td>
</tr>
<tr>
<td>34%</td>
<td>9%</td>
<td>1.55</td>
<td>889</td>
<td>732</td>
<td>634</td>
</tr>
<tr>
<td>35%</td>
<td>10%</td>
<td>1.62</td>
<td>727</td>
<td>598</td>
<td>518</td>
</tr>
<tr>
<td>36%</td>
<td>11%</td>
<td><strong>1.69</strong></td>
<td><strong>605</strong></td>
<td><strong>498</strong></td>
<td>432</td>
</tr>
<tr>
<td>37%</td>
<td>12%</td>
<td>1.76</td>
<td>513</td>
<td>423</td>
<td>366</td>
</tr>
<tr>
<td>38%</td>
<td>13%</td>
<td>1.84</td>
<td>441</td>
<td>363</td>
<td>314</td>
</tr>
<tr>
<td>39%</td>
<td>14%</td>
<td>1.92</td>
<td>337</td>
<td>316</td>
<td>273</td>
</tr>
</tbody>
</table>

C. Power for Secondary and Tertiary Endpoints

C.1. Secondary endpoint

The secondary hypothesis is that the proportion of patients achieving remission will be different in the two augmentation groups. The difference between the two augmentation groups is expected to be less than those estimated for the primary hypotheses comparing augmentation with monotherapy. Therefore, the approach to sample size estimation for the secondary hypothesis will be to determine the minimal difference that can be detected between the two proportions with the sample size determined for the primary hypotheses. As described above, there are no published results on remission using the QIDS-SR16 for augmentation with aripiprazole and there is only one study with remission estimated at 12 weeks or later (Berman 2009), where 36.8% achieved remission in 14 weeks. There is only one published result using the QIDS-SR16 for outcomes for augmentation with bupropion (39% remission) (STAR*D) which is the highest reported remission in patients with refractory depression. Power calculations for this secondary endpoint were based on 39% remission in one augmentation group and varying the reduction in remission in the other augmentation group. The power calculations assumed a 0.05 two-sided significance level and adjusted for a 15% inflation factor for loss to follow-up. With 506 patients per group, if remission in the augmentation with
The aripiprazole group is 30% and remission in the augmentation with bupropion is 39%, there would be approximately 80% power to detect a 9% absolute increase (odds ratio = 1.49) in remission between the augmentation groups. Due to costs and resources, the study cannot be sized to have high power to detect much smaller treatment effects. However, with a sample of 506 per group there would still be 50% power to detect a 6.5% absolute increase (relative odds ratio=1.33), which can be considered a minimal clinical meaningful difference. Therefore, if the actual observed difference between the augmentation groups is as small as 6.5%, the study would detect the difference as statistically significant at the 0.05 significance level. Tables 10 and 11 below summarize the trial’s ability to detect a difference between the augmentation groups varying the remission assumptions.

Table 12. Sample Size Estimation Per Group for Varying Remission at 12 Weeks for One Augmentation Group Compared to 39% Remission at 12 Weeks in the Other Augmentation Group for 50% Power, α=0.05, and adjustment for a 15% Withdrawal Rate

<table>
<thead>
<tr>
<th>Estimated Remission in Augmentation Group 1</th>
<th>Estimated Remission in Augmentation Group 1</th>
<th>Absolute Increase in Remission</th>
<th>Relative Odds Ratio</th>
<th>50% Power α=0.05 Sample Size Per Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>32%</td>
<td>39%</td>
<td>7%</td>
<td>1.36</td>
<td>414</td>
</tr>
<tr>
<td><strong>32.5%</strong></td>
<td><strong>39%</strong></td>
<td><strong>6.5%</strong></td>
<td><strong>1.33</strong></td>
<td><strong>481</strong></td>
</tr>
<tr>
<td>33%</td>
<td>39%</td>
<td>6%</td>
<td>1.30</td>
<td>566</td>
</tr>
<tr>
<td>34%</td>
<td>39%</td>
<td>5%</td>
<td>1.24</td>
<td>820</td>
</tr>
</tbody>
</table>
Table 13. Power Calculations for Varying Remission at 12 Weeks for One Augmentation Group Compared to 39% Remission at 12 Weeks in the Other Augmentation Group for a Fixed Sample Size of 506 per Group, $\alpha=0.05$, and adjustment for a 15% Withdrawal Rate

<table>
<thead>
<tr>
<th>Estimated Remission in Augmentation Group 1</th>
<th>Estimated Remission in Augmentation Group 1</th>
<th>Absolute Increase in Remission</th>
<th>Relative Odds Ratio</th>
<th>No. per Group=506 $\alpha=0.05$</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%</td>
<td>39%</td>
<td>9%</td>
<td>1.49</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>31%</td>
<td>39%</td>
<td>8%</td>
<td>1.36</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>32%</td>
<td>39%</td>
<td>7%</td>
<td>1.36</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td><strong>32.5%</strong></td>
<td><strong>39%</strong></td>
<td><strong>6.5%</strong></td>
<td><strong>1.33</strong></td>
<td><strong>52%</strong></td>
<td></td>
</tr>
<tr>
<td>33%</td>
<td>39%</td>
<td>6%</td>
<td>1.30</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>34%</td>
<td>39%</td>
<td>5%</td>
<td>1.24</td>
<td>33%</td>
<td></td>
</tr>
</tbody>
</table>

b. **Relapse in symptoms after achieving remission or in the Continuation phase:** An important long-term outcome of the study will be whether patients remain in remission or whether symptoms of depression recur. Most studies of depression treatments have focused on the acute treatment phase and not the continuation of treatment. Reports of the proportion of patients that have a relapse of symptoms ranges from about 50% to over 80% depending on the duration of follow-up and definition of relapse. In this study, relapse is defined as the proportion of patients who worsen in symptoms measured by QIDS-C16 $\geq 11$ after achieving remission or who worsen during continuation treatment after 12 weeks of treatment. If 50% of the randomized patients (an average of 253 per group) enter the continuation phase, the trial would have 58% power to detect a 10% reduction (odds ratio = 0.67) in relapse of symptoms from 50% to 40%. If only 40% of the randomized patients (an average of 202 per group) enter the continuation phase, the trial would have 48% power to detect a 10% reduction (odds ratio = 0.67) in relapse of symptoms from 50% to 40%.

c. **Akathisia:** Symptoms of akathisia comprise a part of the side effect profile of antidepressant, but are more prevalent in atypical antipsychotic medications. It is expected that the rate of akathisia will be higher in the aripiprazole augmentation group. In one of the aripiprazole augmentation studies (Berman, 2007), the proportion of patients with akathisia symptoms after 6 weeks was 23.1% in the patients receiving augmentation with aripiprazole and 4.5% for patients receiving placebo and antidepressant monotherapy. Using the assumptions for the difference in
two proportions, a sample size of 506 patients per group, and two-sided tests at the 0.025 level, the study would have 100% power to detect a 12% difference in akathisia from 23% to 5%, and would have 84% power to detect a 8.5% difference between treatment groups from 23% to 14.5%.

C.2. Tertiary endpoints

A power analysis was also performed for the additional depression outcomes that are defined by the QIDS-C\textsubscript{16} score; in particular response and percent change in QIDS-C\textsubscript{16}:

**Response:** Response to treatment measure by the QIDS-C\textsubscript{16} is often defined as a 50% decrease in score and is usually published in parallel with the remission results (Trivedi, 2006; Rush, 2006; Berman 2007). Response to treatment is expected to be a higher than remission but the relative treatment effects are expected to be similar (Nelson and Papakostas, 2009) or slightly smaller (Trivedi, 2006; Rush, 2006). Among the studies used to determine the sample size for the primary hypotheses, response was higher than remission in the shorter term aripiprazole studies, but response was similar to remission in the STAR*D studies. If the relative effects are slightly smaller or the proportion responding is smaller, there will be a modest loss of power for the response outcome compared to remission.

**Percent change in QIDS-C\textsubscript{16} score:** Mean percent change in QIDS-SR\textsubscript{16} from baseline was reported for the STAR*D studies and provides estimates for bupropion monotherapy and for augmentation with bupropion. Percent change in QIDS-SR\textsubscript{16} after 14 weeks was distributed with mean -25.3 (±43.9 std. dev.) for augmentation with BUP-SR and with mean -17.1 (± 49.7 std. dev.) for augmentation with buspirone (Trivedi, 2006). In another study (Rush, 2006), percent change in QIDS-C\textsubscript{16} at 14 weeks BUP-SR monotherapy was reported with a mean -16.4 (± 52.7 std. dev.). If percent change in QIDS-C\textsubscript{16} score is assumed to be normally distributed, power calculations for the difference between two means for two-sided tests at the 0.025 level yields an estimated 75% power to detect a difference of 8.9% (25.3 – 16.4, Std dev = 45.0) between augmentation and monotherapy.
D. Duration of Study and Number of Participating Sites

The study is expected to complete the randomization of at least 1518 patients in 29 months, with up to 36 weeks minimum follow-up of all randomized patients who are randomized within the first 24 months. Participants randomized in the last 5 months of the recruitment period (months 25 to 29) and who enter the continuation phase of the study will be censored (i.e., withdrawn from the study prior to completing 36 weeks of follow-up). If randomization can be completed within 27 months, all randomized participants will be able to be followed for a minimum of 24 weeks (up to 12 weeks in the continuation phase). If randomization cannot be completed in 27 months, then any participants randomized by the end of 29 months will still be able to complete the acute treatment phase and about one month of continuation phase follow-up.

The study was planned to have a maximum of 35 participating sites at any given time with a recruitment goal of randomizing an average of 2.1 participants per month per for up to 24 months, anticipating that some sites would not meet the recruitment goals and would be dropped from the study. The randomization rate was lower than expected in the first 20 months of the trial, and the protocol has been amended to extend the total study duration by 3 months, but allow for up to 5 months to reach the target sample size. In order to complete the randomization of 1518 participants in 29 months, 35 participating sites would be required to randomize 1.5 participants per month (approximately 1 every three weeks) with the target of 44 randomized participants per site. If some sites recruit fewer than the targeted number of participants, other sites will need to randomize more than 44 participants. If the number of sites was reduced to 30, an average of 1.7 randomized participants would be needed per site per month with the target of 51 randomized patients per site.
E. Statistical Analysis

E.1. Interim monitoring and analysis

Interim monitoring will focus on efficacy, safety and feasibility of the study.

E.1.1. Interim Analysis for Potential Early Study Termination for Study Efficacy

One interim look at the primary endpoint of remission in the augmentation groups compared to the bupropion monotherapy group will be proposed to the DMC for making the recommendation about whether or not to continue the trial, or to recommend increasing the sample size. It is proposed that the interim analysis be done when half (~750) of the patients planned for the study have been randomized and followed for the 12 week acute treatment period.

A Haybittle-Peto type boundary (p<0.001) is proposed for monitoring the study for early efficacy. Conditional power will be calculated for the co-primary hypotheses for the purpose of sample size re-estimation and to determine the likelihood of achieving a significant outcome, based on proportion of patients remitting in 12 weeks in the augmentation groups compared to the observed remission in the monotherapy group. The re-estimation procedure will be based on conditional power using the observed treatment effects (Lan and Trust, 1997). Even though the observed treatment effect is used for the sample size re-estimation, this method allows the sample size to be increased during the study without inflating the type I error provided the trial is stopped for futility if the observed conditional power is less than the predefined lower limit. The proposed conditional power re-estimation rules are:

1. If the observed conditional power (CP) is \( \leq C_L \) (CP lower limit), stop the trial for futility.
2. If CP is \( > C_U \) (CP upper limit), continue to the scheduled end of the trial.
3. If \( C_L < CP < C_U \), adjust the sample size so that the conditional power under the observed trend is at least 0.80.

To fully preserve the type I error, the interim analysis should be done prior to an information fraction of 0.70 (70% of target intake) and the lower limit on conditional power should be at least 10%. The proposed lower limit must be set prior to unblinding the data. The proposed lower limit of conditional power for this study is 25% for both augmentation groups compared to
monotherapy under the trends observed at the interim analysis. However, the Data Monitoring Committee (DMC) will be requested to approve or reset this lower limit prior to conducting the analysis. In addition, the DMC recommendation of early termination of the study will include information on secondary outcomes, safety and relevant external information. If the conditional power is $> C_l$ and $< C_u$, then the DMC will have the option of recommending and increase in sample size so that the conditional power under the observed trend is at least 0.80.

E.1.2. Safety Monitoring

Trial safety will be monitored by CSPCC and the Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC) and the Study Chairs’ Offices throughout the study. Safety reports will be submitted to the Data Monitoring Committee (DMC) approximately every 6 months after enrollment begins, or more frequently if requested by the DMC. In addition, an independent central medical monitor is planned for CSP who will review all serious adverse events occurring during the study for accuracy of diagnosis and relatedness to the study medications. For reports to the DMC closed session, serious adverse events will be summarized by treatment group, FIBSER and diagnostic criteria (based on MedDRA coding) and relatedness to the assigned study medications. Any serious adverse event that is unexpected and possibly related to the intervention will be submitted to all the study sites as a safety alert.

The proportion of patients experiencing an SAE in each treatment group will be calculated for each treatment group and the proportions will be compared between treatment groups using a chi-square test for the difference in proportions and will be tested at the 0.05 level. If the proportion of SAE is significantly higher in one treatment group compared to another, the DMC may consider recommending that recruitment in the trial, or one arm of the trial, be stopped, or that the dosing protocol be modified. Since there is no placebo comparator group in this study, the proportion of SAE occurring in a treatment group will need to be assessed relative to the expected safety protocol for the medications involved. An SAE rate higher than expected may also lead the DMC to recommend that recruitment in the trial, or one arm of the trial, be stopped, or that the dosing protocol be modified.
E.1.3. Final analysis

Baseline Comparability

The distribution of baseline patient characteristics between the randomization groups will be evaluated using descriptive statistics, confidence intervals and graphical methods.

A list of baseline variables that may be potential risk factors of poor outcome will be identified a priori for use in covariate adjustment. These will be identified before the final analysis and will include age at randomization, history of the number of antidepressant regimens tried and failed prior to enrollment in the trial, duration of the index depressive disorder, baseline scores from the QIDS-C_{16} and other associated conditions such as anxiety.

Description of Patients Screened

For all screened patients, the reasons that patients with a diagnosis of major depression were not eligible, or if eligible, elected not to consent or be randomized will be summarized in a table listing the study inclusion and exclusion criteria and consent status.

Analysis of Primary Outcome Measure

The primary outcome of remission during the first 12 weeks after randomization will be analyzed using a logistic regression model. The analyses for the co-primary hypotheses will compare the proportion of patients in remission in each augmentation treatment group compared to the proportion of patients in remission in the bupropion monotherapy group. One logistic regression model will be set up with treatment indicator variables to test for treatment effects of each of the augmentation groups compared to the monotherapy group. The regression model will also include study site as a stratification variable. These analyses will be done according to the intent-to-treat principle, that is, according to the original treatment assignment, regardless of adherence to the assigned medication regimen.

Remission will be determined by a QIDS-C_{16} score of 5 or less on two consecutive visits. Scheduled visits during the acute phase are 2 weeks apart so the first remission case cannot occur until 4 weeks of follow-up have occurred. The number of patients in remission at 12 weeks will be determined by counting the number of patients who achieved the remission criteria at any
time during the 12 weeks though it is possible that the QIDS-C16 score will be greater than 5 at 12 weeks for a patient who has achieved remission. The denominator for the proportion of patients in remission will be the number of patients randomized to the treatment group. Patients who are lost to follow-up or who leave the study due to side effects or due to failure to improve on the assigned regimen will be counted as treatment failures (i.e., not having achieved remission). Sensitivity analyses will be performed where 1) the patients who are withdrawn from the study are removed from the denominator of the remission calculation, and 2) patients who achieve remission but worsen in QIDS-C16 score above 5 by 12 weeks, to assess the impact of these two factors on the primary remission analysis.

The two co-primary hypotheses will be tested using the sequentially rejective procedure of Hochberg (Hochberg, 1988) with a familywise Type I error rate of 0.05 level for 2-sided tests. The p-values for the results of the two hypotheses test that \( H_0: \text{relative risk} = 1.0 \) will be ordered from the largest to the smallest. The test result with the largest p-value will be assessed at the 0.05 (two-sided) significance level, and if it is less than 0.05, all comparisons are declared to be significant; otherwise the result with the smallest p-value will be assessed at the 0.025 (two-sided) significance level.

In addition to stratifying the analysis by site, a risk covariate will be considered for inclusion in the logistic regression model for the primary analysis to adjust for whether the patient had failed on one or more antidepressant regimens (treatment resistant) for the episode of depression concurrent with randomization.

**Analysis of Secondary Outcomes**

Treatment effectiveness will be assessed by comparing remission, response and relapse between treatment groups. Safety will be assessed by side effects, tolerability and discontinuation; and costs are assessed by direct costs of care and health care utilization. All statistical tests will be two-sided with the significance level adjusted for multiple comparisons when two tests are being performed for augmentation vs. monotherapy.
**Hypothesis 2.a.** Remission at 12 weeks in antidep + BUP-SR group will be compared with remission in the antidep + ARI using the same logistic regression methodology described for primary hypotheses. The treatment effect for antidep + BUP-SR vs. antidep + ARI will be evaluated at the 0.05 significance level as the second family of comparisons after testing the primary hypothesis. To perform this test at the 0.05 level, at least one of the tests for the co-primary hypotheses must be statistically significant. In other words, if there is not a significant effect of at least one of the augmentation groups compared to BUP-SR monotherapy, this test will not be performed.

**Hypothesis 2.b-d:** Relapse (QIDS-C_{16} ≥11) within 36 weeks after the initiation of treatment among participants achieving remission in the acute treatment phase will be compared between each of the augmentation groups and BUP-SR monotherapy at the 0.025 significance level and between the two augmentation groups at the 0.05 significance level (antidep + BUP-SR vs. antidep + ARI) using time-to-event life-table methodology where the analysis will be based on the time from remission to relapse among those participants who achieve protocol remission in the acute treatment phase (See the Time to Relapse section below).

Relapse of symptoms (QIDS-C_{16} ≥11) among those participants who enter the continuation phase (QIDS-C_{16} <11) and did not remit in the acute treatment phase will be compared between each of the augmentation groups and BUP-SR monotherapy at the 0.025 significance level and between the two augmentation groups at the 0.05 significance level (antidep + BUP-SR vs. antidep + ARI) using time-to-event life-table methodology where the analysis will be on the time from entering the continuation phase to the relapse of symptoms (See the Time to Relapse section below).

Alternative representations of the relapse outcomes will also be presented using conditional logistic regression that will include both the remission and relapse outcomes.

**Hypothesis 2.e:** A safety outcome is included as an important secondary hypothesis because of the increased risk of serious side effects irrespective of treatment effect on symptoms. The proportion of patients who develop akathisia, other akathisia-like side effects (e.g., tremor,
irritability, motor restlessness) and extrapyramidal side effects will be compared between the augmentation groups. The composite akathisia symptom and extrapyramidal side effects count will be tested at the 0.025 significance level for each of the augmentation groups vs. BUP-SR monotherapy and between the two augmentation groups at the 0.05 significance level (antidep + BUP-SR vs. antidep + ARI) using the logistic regression methodology described for the primary hypotheses.

**Hypothesis 2.f:** Costs of medications and health care utilization during the 36 week follow-up will be determined by the methods described in Section XVIII, Cost Effectiveness. The costs and cost effectiveness of treatment in augmentation groups will be compared with the BUP-SR monotherapy group, and the augmentation groups compared with each other (antidep + BUP-SR vs. antidep + ARI) using the methodologies defined in Section XVIII. The impact of treatment on other economic outcomes including employment and productivity will also be included in the cost-effectiveness analyses.

**Additional Analyses**

Treatment comparisons for the additional analyses will be evaluated with the same approach as the secondary analyses (unless otherwise indicated below). Comparisons of the augmentation groups with BUP-SR monotherapy will be evaluated at the 0.025 level and the comparison of the two augmentation groups (antidep + BUP-SR vs. antidep + ARI) will be evaluated at the 0.05 level. These outcomes will be supportive of the primary and secondary analyses.

**Tertiary Objective 1: Response**  
The proportion of patients who achieve protocol response to treatment will be compared separately for the two protocol specified measures of response (i.) a 50% decrease in QIDS-C16 score from baseline score, and (ii.) achieving a CGI-Improvement score of 1 or 2 during follow-up) between treatment groups using the multiple logistic regression methodology described for the primary analysis. This threshold outcome is usually presented in conjunction with remission. It will be treated in this study as a supportive outcome measure.

**Tertiary Objective 2: Percent change in QIDS-C16 score:** Mean percent change in QIDS- C16 from baseline will be compared between treatments using analysis of variance methodology.
While the distribution of percent change in QIDS-C16 score is not continuous and may not be normally distributed, a parametric approach will be used unless there are major deviations from normality, and in that case, non-parametric methods will be used.

**Tertiary Objective 3: Discontinuation of Treatment:** The proportion of patients who discontinue treatment due to lack of tolerance of the drug will be compared between treatment groups using logistic regression methodology similar to the primary analysis. Discontinuation of treatment could be due to inability to tolerate the drug due to side effects or due to lack of treatment response in the acute phase leading to the patient to be withdrawn from the study and switched to another treatment option.

**Tertiary Objective 4: Additional Acute Phase Outcomes:** Treatment comparisons will also be performed among the three regimens to assess the relative treatment effect on other associated features of depression (e.g., anxiety; suicidal ideation; function; quality of life; attrition due to side effects; overall side-effect burden; and other specific side effects, such as changes in BMI) during the acute treatment phase (Randomization to 12 weeks). A mixed effects repeated measures model will be used to assess treatment effects on patient assessment scores for these features (i.e., from the PHQ-9, CGI-S, CGI-I, and FIBSER) using the baseline response for these measures as a covariate. For assessments that are only recorded at baseline and at 12 weeks an analysis of covariance model will be used to assess the treatment effects on these measures (e.g., Columbia suicide ideation, Beck Anxiety Index) with the baseline response for these measures included as a covariate.

**Tertiary Objective 5: Additional Long-Term Outcomes** Treatment comparisons will also be performed for long-term outcomes for the 24 week period following the acute treatment phase among the three regimens in terms of a change in associated features (e.g., anxiety; suicidal ideation; function; quality of life; attrition due to side effects; overall side-effect burden; extrapyramidal symptoms and other specific side effects, such as changes in BMI).

**Assessment of Treatment Response at Each Scheduled Visit:** In addition to the 12 and 36 week evaluations the key descriptive measures for symptoms of depression (remission, response
percent change in QIDS-C16, relapse) will be assessed at each scheduled visit. Treatment comparisons will be performed and the results will be presented in tables and plots as the proportion (or mean percent change) ± the standard error for each treatment group and as the relative difference between groups (odds ratio and 95% CI).

**Time to Remission:** The Kaplan-Meier product limit method will be used to estimate cumulative time to remission after randomization. The analysis will be stratified by site and will test differences between treatment regimens for time to remission (QIDS-C16 ≤ 5 on 2 consecutive visits). The primary period for comparisons will be 0 to 12 weeks, however, the period from 12 weeks to 36 weeks will also be assessed. After 12 weeks remission will be determined by QIDS-C16 ≤ 5 at one visit because visits are 4 weeks apart. Since there are wider intervals during that period, there will be more interval censoring and ties. In an exploratory analysis, a Cox proportional hazards model will be used to adjust for the following pre-specified baseline covariates: age, sex, history of the number of antidepressant regimens tried and failed prior to enrollment in the trial, duration of the index depressive disorder, baseline scores from the QIDS-C16 and other associated conditions or symptoms of depression to assess whether these baseline variables have an impact on the treatment effect. The Cox proportionality assumption will be assessed prior to fitting this model.

**Time to Relapse:** The Kaplan-Meier product limit method will also be used to estimate cumulative time to relapse among those patients who achieved remission after randomization and, separately, among those participants who enter the continuation phase. The analyses, which will be stratified by site, will test differences between treatment regimens for time to relapse. Among participants who achieve protocol remission in the acute treatment phase, the time-to-event analysis will be based on the time from protocol remission in the acute treatment phase to the time to relapse of symptoms (QIDS-C16 ≥ 11) during up to 36 weeks of follow-up post-randomization. In the analysis of the continuation phase, participants who did not remit in the acute treatment phase will be counted as relapsed if QIDS-C16 ≥ 11, and the time-to-event analysis will be based on the days from entering the continuation phase to the day that relapse of symptoms was determined. Since there are wider intervals between scheduled assessments during the continuation phase, there will be more interval censoring and ties. However, relapse
events may be reported between visits if the patient presents to the clinic with worsening symptoms. In an exploratory analysis, a Cox proportional hazards model will be used to adjust for the following pre-specified baseline covariates: age, sex, history of the number of antidepressant regimens tried and failed prior to enrollment in the trial, duration of the index depressive disorder, baseline scores from the QIDS-C\textsubscript{16} and other associated conditions or symptoms of depression to assess whether these baseline variables have an impact on the treatment effect. The Cox proportionality assumption will be assessed prior to fitting this model.

**General Quality of Life:** Summary scores will be calculated for the QOL measure (Q-LES-Q). A repeated measures model will be used to perform an analysis of covariance to assess the effects of treatment, time, covariates, and for any treatment by time interaction. If there is a significant treatment by follow-up time interaction, comparisons between treatments at each follow-up visit will be performed using t-tests with a 0.01 significance level.

**Analysis of Safety Data**
The proportion of patients experiencing an SAE will be calculated for each treatment group. A chi-square test for the difference in proportions will be used to compare treatment groups over all SAE at the 0.05 level, and with subgroupings of SAE or non-serious AE at the 0.01 significance level to adjust for multiple comparisons. Treatment comparisons will be made for the number of patients experiencing a SAE, the number if treatment-related SAE, the number of SAE by diagnostic groups (based on MedDRA coding) by category on the FIBSER, and for the non-serious adverse effects pre-specified by the protocol.
XXIV. FEASIBILITY WITHIN THE VA SYSTEM

A. Estimates of Patient Availability
The target sample size for the study is a total of 1518 patients to be randomized over a 29 month period. There will be 30-35 sites participating in the trial and each will have a target of 51 randomized patients (an average of 2.1 patients per site). It is conservatively estimated that 1 in every 10 patients diagnosed with major depression who are screened for the study will be randomized. Therefore, each site would need to have a population of at least 510 patients with major depression from which to recruit.

The VA Health Economic Resource Center (HERC) conducted a review of VA inpatient, outpatient, and pharmacy utilization records from FY 2009 to identify the number of unique patients who were treated in the VA system for depression and met the following criteria:
   a.) At least one inpatient or at least two outpatient visits to a medical center in FY 2009 with a diagnosis of major depression (selecting on ICD-9 diagnostic codes: 311, 296.82, 296.2, 296.3, 296.9, 300.4).
   b.) Exclude patients with a diagnosis of schizophrenia.
   c.) Exclude patients with a diagnosis of bipolar disorder.
   d.) Exclude patients with a diagnosis of dementia.
   e.) Exclude patients who had a prescription of bupropion, aripiprazole, or lithium during FY2009.
   f.) Include patients with home address (zip code) within 90 miles (within approximately 1.5 hours of travel time) of the VA medical center.

Using FY2009 utilization files (inpatient, outpatient), there were 570,234 patients diagnosed with depression in the VA system. Supplemented with information from the FY2009 DSS Outpatient Pharmacy and filtering out patients with schizophrenia, bipolar disorder, dementia, or patients taking medications such as bupropion, aripiprazole, or lithium, reduced the depression cohort to 398,832 patients. Further excluding patients where distance could not be determined (827), the depression cohort contacted to 398,005 patients. Lastly, limiting the travel time to < 1.5 hours from the medical center resulted in a final potentially eligible cohort of 329,615 patients in the VA system.
The numbers of unique patients at each VAMC that met the selection criteria for this search are listed in the table below for 128 VA Medical Centers. The table rows are ordered by the number of potentially eligible patients in descending order. At the top 60 VA medical centers, there are more than 2000 patients meeting the screening criteria. If we conservatively assume that 50 percent of the patients who were seen in the clinic achieved remission and were in continuing care, a site with 1000 patients would have approximately 500 patients available for screening. Therefore, only 10 percent of the potentially eligible patients at each site would need to be randomized to meet the target of 51 randomized participants per site. There would also additional patients presenting with a new diagnosis of depression during the course of the recruitment period. Forty-one (32%) of the VA medical centers have more than 2000 patients who live within 30 miles of the medical center, and 78 (61%) have more than 1000 patients in that proximity. Of the 45 VA medical centers that have indicated interest in participating in this study, 26 potential sites have more than 2000 potentially eligible patients living within 30 miles of the medical center and 37 have more than 1000 potentially eligible patients. Based on these patient availability numbers, we believe that the recruitment goal is realistic and achievable in a 24 month period.
Table 14. VA Patient Count of Selected Cohort File Patients Diagnosed With Depression in FY2009 Summarized By VA Medical Center and Distance from VA Medical Center

<table>
<thead>
<tr>
<th>Medical Center Location</th>
<th>Zip Code within 90 miles of VA Medical Center</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Distance 0 - 30 Miles</td>
</tr>
<tr>
<td>(671) SAN ANTONIO, TX</td>
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</tr>
<tr>
<td>(642) PHILADELPHIA, PA</td>
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</tr>
<tr>
<td>(580) HOUSTON, TX</td>
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<tr>
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<tr>
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<td>x</td>
</tr>
<tr>
<td>(663) VA PUGET SOUND, WA</td>
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</tr>
<tr>
<td>(691) WEST LOS ANGELES, CA</td>
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</tr>
<tr>
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<td>(554) DENVER, CO</td>
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<tr>
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<td>(605) LOMA LINDA, CA</td>
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<tr>
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<tr>
<td>(688) WASHINGTON, DC</td>
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<tr>
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<tr>
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<tr>
<td>(537) CHICAGO (W.SIDE), IL</td>
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<tr>
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<tr>
<td>(695) MILWAUKEE, WI</td>
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<tr>
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<tr>
<td>(546) MIAMI, FL</td>
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<tr>
<td>(512) BALTIMORE HCS, MD</td>
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<tr>
<td>(589) KANSAS CITY, MO</td>
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</table>
Table 14 (Cont’d). A Patient Count of Selected Cohort File Patients Diagnosed With Depression in FY2009 Summarized By VA Medical Center and Distance from VA Medical Center

<table>
<thead>
<tr>
<th>Medical Center Location</th>
<th>Zip Code within 90 miles of VA Medical Center</th>
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<tbody>
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<td></td>
<td>Distance 0 - 30 Miles</td>
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<tr>
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<tr>
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<tr>
<td>(646) PITTSBURGH, PA</td>
<td>x</td>
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<tr>
<td>(650) PROVIDENCE, RI</td>
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<tr>
<td>(528) BUFFALO, NY</td>
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</tr>
<tr>
<td>(516) BAY PINES, FL</td>
<td>x</td>
</tr>
<tr>
<td>(590) HAMPTON, VA</td>
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<tr>
<td>(757) COLUMBUS, OH</td>
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</tr>
<tr>
<td>(561) NEW JERSEY HCS, NJ</td>
<td></td>
</tr>
<tr>
<td>(635) OKLAHOMA CITY, OK</td>
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<tr>
<td>(614) MEMPHIS, TN</td>
<td>x</td>
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<tr>
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<tr>
<td>(595) LEBANON, PA</td>
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<tr>
<td>(689) VA CONNECTICUT HCS, CT</td>
<td>x</td>
</tr>
<tr>
<td>(640) PALO ALTO, CA</td>
<td>x</td>
</tr>
<tr>
<td>(521) BIRMINGHAM, AL</td>
<td>x</td>
</tr>
<tr>
<td>(674) TEMPLE, TX</td>
<td>x</td>
</tr>
<tr>
<td>(565) FAYETTEVILLE, NC</td>
<td></td>
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<tr>
<td>(626) MIDDLE TENNESEE HCS, TN</td>
<td></td>
</tr>
<tr>
<td>(593) LAS VEGAS, NV</td>
<td>x</td>
</tr>
<tr>
<td>(652) RICHMOND, VA</td>
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<tr>
<td>(552) DAYTON, OH</td>
<td>x</td>
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<td>(558) DURHAM, NC</td>
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<td>(629) NEW ORLEANS, LA</td>
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<td>(596) LEXINGTON, KY</td>
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<td>(659) SALISBURY, NC</td>
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<td>(531) BOISE, ID</td>
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<tr>
<td>(573) GAINESVILLE, FL</td>
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<tr>
<td>(632) NORTHPORT, NY</td>
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</table>
Table 14 (Cont’d). A Patient Count of Selected Cohort File Patients Diagnosed With Depression in FY2009 Summarized By VA Medical Center and Distance from VA Medical Center

<table>
<thead>
<tr>
<th>Medical Center Location</th>
<th>Zip Code within 90 miles of VA Medical Center</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Distance 0 - 30 Miles</td>
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<tr>
<td>(534) CHARLESTON, SC</td>
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<tr>
<td>(556) NORTH CHICAGO, IL</td>
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<tr>
<td>(517) BECKLEY, WV</td>
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<tr>
<td>(662) SAN FRANCISCO, CA</td>
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</tr>
<tr>
<td>(526) BRONX, NY</td>
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</tr>
<tr>
<td>(544) COLUMBIA, SC</td>
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<tr>
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<tr>
<td>(581) HUNTINGTON, WV</td>
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<tr>
<td>(506) ANN ARBOR, MI</td>
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<tr>
<td>(570) FRESNO, CA</td>
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<td>(613) MARTINSBURG, WV</td>
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<tr>
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<tr>
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<td>x</td>
</tr>
<tr>
<td>(667) SHREVEPORT, LA</td>
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<tr>
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<tr>
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<td>(654) RENO, NV</td>
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</table>
Table 14 (Cont’d). A Patient Count of Selected Cohort File Patients Diagnosed With Depression in FY2009 Summarized By VA Medical Center and Distance from VA Medical Center

<table>
<thead>
<tr>
<th>Medical Center Location</th>
<th>Zip Code within 90 miles of VA Medical Center</th>
<th></th>
<th></th>
<th></th>
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</thead>
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<td>Distance 31 - 60 Miles</td>
<td>Distance 61 - 90 Miles</td>
<td>Total</td>
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<tr>
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<tr>
<td>(459) HONOLULU, HI</td>
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<td>13</td>
<td>627</td>
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<tr>
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<td>12</td>
<td>745</td>
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<tr>
<td>(679) TUSCALOOSA, AL</td>
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<td>600</td>
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<td>139</td>
<td>871</td>
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<tr>
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<tr>
<td>(519) BIG SPRING, TX</td>
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<td>620</td>
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<tr>
<td>TOTAL</td>
<td>202,577</td>
<td>82,921</td>
<td>44,117</td>
<td>329,615</td>
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NOTE:  x = Site interested in participating in CSP#576
XXV. STUDY ORGANIZATION AND ADMINISTRATION

A. Monitoring Bodies
The groups charged with monitoring the various aspects of the study will be the Executive Committee, the Data Monitoring Committee (DMC) and the West Haven Human Rights Committee. These committees will meet at regular intervals according to the current Cooperative Studies Program guidelines: prior to the beginning of patient intake and at least every twelve months thereafter. In addition, the CSP Site Monitoring, Auditing and Resource Team (SMART), located at the CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC), will monitor the trial for GCP compliance.

The Executive Committee is the management and decision-making body for the operational aspects of the study and will monitor the performance of participating medical centers and the quality of data collected. The Executive Committee will formulate publication plans and will oversee the publication and presentation of all data from the study. The Committee must grant permission before any study data may be used for presentation or publication.

The Data Monitoring Committee (DMC) will review the progress of the study and will monitor patient intake, outcomes, adverse events, and other issues related to patient safety. The DMC makes recommendations to the Director of the Clinical Science Research and Development (CSRD) Service about whether the study should continue or be stopped. The DMC will consist of experts in the fields of psychiatry, biostatistics, and ethics. These experts will not be participants in the trial and will not have participated in the planning of the protocol. The DMC will consider safety or other circumstances as grounds for early termination, including either compelling internal or external evidence of treatment differences or the unfeasibility of addressing the study hypothesis (e.g., poor patient intake, poor adherence to the protocol).

At each of its meetings during the study period, the DMC will review the randomization rates and assess the difference between the actual and the projected rates, as well as the impact of these assessments on overall trial size. If the study recruitment is inadequate, the reasons for exclusion may be scrutinized and actions may be suggested. An assessment of whether the trial should be continued will be made followed by recommendations, as appropriate. All serious
adverse events will be reported on a regular basis to the DMC for their review. Unexpected serious adverse events will be reported to the DMC as soon as they become known based upon the consensus of the Study Chair, the Study Biostatistician, the Director, West Haven CSPCC, and the Albuquerque CSPCRPCC. The Study Biostatistician will provide the appropriate data to the DMC at specified intervals for this purpose. Conditional power estimates will be provided to the DMC to assist them in making their decisions and recommendations.

The Human Rights Committee (HRC) at the Coordinating Center will review the study prior to its initiation to ensure proper protection of patients’ rights and safety. The role of the CSPCC HRC is being rechartered by the CSP. However, it is expected that if the HRC is reconstituted prior to study initiation, the HRC will review the study prior to initiation to ensure proper protection of patient's rights and safety. To ensure that the safety and rights of research volunteers are being properly protected, a member of the HRC at WH-CSPCC will conduct at least one site visit to a participating medical center during the course of the study. These HRC visits will include interviews of study participants.

CSP SMART will provide GCP training at the kick-off meeting and will conduct initiation visits at all sites. It also will conduct GCP site review and a for cause audit of a participating site if requested by any of the monitoring bodies. If an IND or IDE is required by the FDA, the frequency of follow-up monitoring visits will be determined in consultation with the FDA. At a minimum each site will be visited at least once during the study by SMART.

The Study Group, which consists of all participating investigators and study personnel, will meet annually and periodically by teleconference to discuss the progress of the study and any problems encountered during the conduct of the trial.
XXVI. PUBLICATIONS

A. Publication Policy

According to the policy of the Cooperative Studies Program, outcome data will not be revealed to the Study Chairs or participating site investigators until the data collection and clean-up phase of the study is completed. This policy safeguards against possible biases affecting the data collection.

All presentations and publications from this study will follow CSP policy as stated in the CSP Guidelines. The presentation or publication of any or all data collected by site investigators on subjects entered into CSP #576 is under the direct control of the Executive Committee. No individual site investigator has the right to perform analyses, make interpretations, make public presentations, or seek publication of any or all of the data without the approval of the Executive Committee.

The Executive Committee has the authority to establish one or more publication committees (usually comprised of subgroups of site investigators and some members of the Executive Committee) for the purpose of producing manuscripts for presentation and publication. A presentation or publication, formulated by the Executive Committee or its authorized representatives, should be circulated to all members of the Executive Committee for review, comments, and suggestions at least four weeks prior to submission of the manuscript to the presenting or publishing body.

All publications must give proper recognition to the study’s funding source, including the Department of Veterans Affairs Cooperative Studies Program, and should list or reference all principal and site investigators in the study. All VA investigators will list VA as their primary institutional affiliation. Submission of manuscripts or abstracts must acknowledge the work as “a Department of Veterans Affairs Cooperative Study.” A copy of the letter to the editor and the manuscript/abstract submitted for publication or presentation should be sent to the CSP Director and for information purposes to the members of the study’s DMC. The CSP also requires that every manuscript be reviewed and approved by the WH-CSPCC Director and the CSRD Director prior to submission for publication.
B. Planned Publications

An intended plan of the main publications is given below:

<table>
<thead>
<tr>
<th>Manuscript</th>
<th>Projected Time of Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>1 year after study begins</td>
</tr>
<tr>
<td>Primary results</td>
<td>6-12 months after the end of the study</td>
</tr>
<tr>
<td>Long-term effectiveness and safety</td>
<td>12-18 months after the end of the study</td>
</tr>
<tr>
<td>Baseline quality of life, employment, social adjustment</td>
<td>6-9 months after randomization ends</td>
</tr>
<tr>
<td>Association of prior year costs with baseline depression measures</td>
<td>6-9 months after randomization ends</td>
</tr>
<tr>
<td>Costs and cost-effectiveness of three treatment arms</td>
<td>12-18 months after end of follow up</td>
</tr>
<tr>
<td>Employment, social adjustment of three treatment arms</td>
<td>12-18 months after end of follow up</td>
</tr>
<tr>
<td>Baseline anxiety and outcome</td>
<td>12-18 months after end of follow up</td>
</tr>
<tr>
<td>Early-life adversity and outcome</td>
<td>12-18 months after end of follow up</td>
</tr>
<tr>
<td>Medical co-morbidity and outcome</td>
<td>12-18 months after end of follow up</td>
</tr>
<tr>
<td>Other moderators and mediators of outcome and short and long term effectiveness, safety and costs</td>
<td>12-18 months after end of follow up</td>
</tr>
<tr>
<td>Representative vs. highly selected participants in a second step depression treatment trial</td>
<td>12-18 months after end of follow up</td>
</tr>
</tbody>
</table>
XXVII. SUBSTUDY POLICY

The following guidelines have been developed in accordance with the Cooperative Studies Program policies for sub-studies to CSP#576.

1. Any study specifically involving patients who enrolled in this study will be considered a sub-study, even if it is limited to one site. Sub-studies will normally involve collection of additional data. Most ‘ancillary’ analyses of currently collected data (e.g., mediators or moderators of depression outcomes) are already planned as part of the primary study.

2. Requests to perform sub-studies will be accepted only from Site Investigators at any of the designated study sites. Requests should be submitted initially as a letter of intent addressed to the Study Chairs. The letter should specify the objectives and general design of the proposed research, the proposed number of subjects and study sites, and an estimate of the funding, if any, that will be required.

3. Letters may be submitted at any time, but no study will be approved before the end of the first year of the primary study in order to ensure that recruitment is not hindered by the additional workload.

4. The Study Chairs and the Biostatistician will review letters of intent. Although the scientific merit of the study will be considered, the primary purpose of this initial review is to establish that the proposal in no way conflicts with the conduct of the primary study. Recruitment success and the overall performance of the proponent’s site (and any proposed collaborating sites) will be one of the factors considered in this review. Sites that are struggling to meet recruitment goals for the primary study will be considered poor candidates for sub-studies.

5. If the proposal is acceptable, the proponents will be asked to submit a formal study protocol (including a human consent form, if appropriate) and a budget.

6. The Executive Committee, and possibly one or two additional reviewers with expertise in the area of interest, will review the protocol. The purpose of this review is to determine the scientific merit of the study and to determine if the proposed ancillary study conflicts with the goals and/or conduct of the primary study. All substudies require approval by
the DMC and CRADO. Based on the required reviews, proposals will either be approved or disapproved.

7. Locating funding for approved studies is the responsibility of the proponents.

8. Any publications (including abstracts) resulting from substudies must conform to publication policies of the VA Cooperative Studies Program, as specifically outlined for CSP#576. This includes statistical review by the West Haven Coordinating Center and adherence to authorship policies. The proponent of the substudy will normally serve as the principal author of any resulting manuscripts.
XXVIII. REFERENCES


APPENDIX A. HUMAN RIGHTS CONSIDERATIONS

A. Human Rights Committee Review

As of January 22, 2010, the role of the West Haven CSPCC Human Rights Committee (HRC) was changed and, at the time of this submission, review of the initial protocol by the HRC prior to CSSEC was not required. The role of the CSPCC HRC is being rechartered by the CSP. The HRC was not reconstituted prior to study initiation, therefore, the HRC did not review the study prior to initiation. However, the CSPCC HRC has been given a synopsis of the CSP#576 and has been informed of the study progress. The CSP #576 informed consent document will be submitted to the CSP Central IRB for review.

B. Informed Consent Form

The text for the CSP #576 informed consent is on the following pages. This text will be inserted into the VA 10-1086 informed consent template and identified as Form 7.
INTRODUCTION
You are being invited to take part in a research study that is being funded by the Department of Veterans Affairs. Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits you might receive.

Read the information below carefully, and discuss it with family and friends if you wish. Ask one of the study staff if there is anything that is not clear or if you would like more details. Take your time to decide. If you do decide to take part, your signature on this consent form will confirm that you received all of the information below, and that you were able to discuss any questions and concerns you had with a member of the study team.

BACKGROUND AND PURPOSE
This is a study about the treatment of major depression. Major depression involves seriously depressed mood, and/or decreased interest or pleasure.

Although there are several treatments for depression, research is needed to help decide what treatments work best after a person has tried one antidepressant medication (antidepressant) that did not completely improve all depression symptoms. This study is being done to compare three ways to treat major depression after treatment with at least one antidepressant alone has not fully succeeded in improving the symptoms. The cost of the three different treatments will also be compared.

You are being asked to participate because you have major depression and have been taking an antidepressant but you still have some symptoms of depression. Also, based on a screening of your VA medical records, you do not have other medical or mental health problems that might make it difficult for you to participate in this study. For safety reasons, women who are pregnant or plan to become pregnant in the next 9 months may not participate in this study.

If you agree to be in this study and if you pass all screening procedures, your antidepressant medications will be changed to one of three treatments:

a) Switching your treatment to a different antidepressant, which is named bupropion SR (SR means sustained release). Bupropion SR is available as a brand name medication (Wellbutrin SR®).

b) Keeping you on the antidepressant you were taking before starting the study and adding bupropion SR.
c) Keeping you on the antidepressant you were taking and adding an antipsychotic medication called aripiprazole. Aripiprazole is also known as Abilify®. Aripiprazole has been shown to improve major depression when taken with an antidepressant after the antidepressant alone did not work.

Bupropion SR is approved by the Food and Drug Administration (FDA) to treat major depression, and aripiprazole is approved by the FDA to be used in combination with an antidepressant to treat major depression. We don’t know if bupropion SR alone or either drug in combination with other antidepressants will work best.

All three of these treatment options have been found to help some people and are often used to treat depression. By doing this research, we hope to compare how well these options work, and to assess their safety, over a longer treatment period of up to nine months.

This study will include 1518 Veterans from up to 35 different VA medical centers. About 51 Veterans from your VA facility will be asked to participate. There will be 506 participants randomized (like with a flip of a coin) to receive one of the three study treatments.

This study is funded by the VA Cooperative Studies Program, a branch of the VA’s research program that conducts large medical or clinical studies involving more than one VA Medical Center.

**DURATION OF THE RESEARCH**

This entire research study is expected to take approximately three years. If you agree to participate, your participation could last up to 36 weeks (9 months). There are a total of 8 to 14 study visits, depending on your response to the treatment.

During the first 12 weeks of the study, you will come in for the baseline appointment and seven additional visits. If the treatment helps your depression, you will be asked to continue in the study for another 24 weeks. During that time, you will come in for visits every 4 weeks, for an additional 6 visits, yielding a total of 14 visits. All of these visits will be from 30-90 minutes long.

Once you have completed your participation in the study, the study staff will ask you to complete one last interview. After the last interview, you will no longer be in the study and will be referred to your personal clinician for treatment.
STUDY PROCEDURES

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

A study coordinator will review your medical record for information about your symptoms of depression, other medical and mental health problems, your use of medications, and other information that is directly related to the study. About 1 tablespoon of blood will be drawn every 12 weeks to find out if the study medications may be causing problems with your liver or kidneys. For women of child-bearing age, less than one ounce of urine will be collected for a pregnancy test before you can enter the study.

The first study visit involves completing questionnaires that ask about psychiatric symptoms you have, medications you are taking, antidepressants that you have tried in the past, and your general well-being and quality of life. You will also be asked to complete questionnaires that will ask about sexual functioning, adverse childhood experiences, substance abuse and military history. This part of the study should take about 1 to 1 ½ hours. You may skip questions that you do not want to answer.

You may not be able to continue in the study if the questionnaires completed in the first visit show that:

- You are taking bupropion SR or aripiprazole now or have in the past and it has not helped you;
- You have been diagnosed with dementia, psychotic disorder, bipolar disorder, eating disorder or a seizure disorder;
- You have a serious problem which may require hospitalization;
- You need detoxification for drug or alcohol dependence;
- You take medications that should not be taken with aripiprazole or bupropion SR;
- You are currently participating or have participated in another study in the last 30 days;
- You are pregnant or breastfeeding or plan to become pregnant in the next 9 months.

If you are able to continue in the study, the method for deciding which treatment you will be on is like a flip of a coin randomly chosen by a computer program. The decision will not be based on any information about you. Neither you nor the study staff will have any influence in your treatment assignment.
The study procedures for each of the three possible treatments are described below.

1. If you are assigned to change from one antidepressant to another, the antidepressant you are taking now will be slowly decreased and then stopped. At the same time, bupropion SR will be started and then slowly increased. The study doctor will plan with you the steps to decrease and then stop your old antidepressant. It may take as long as 4 weeks before you are only taking bupropion SR. Bupropion SR will be started at 150 mg a day for the first week and then slowly increased over the next few weeks up to a maximum dose of 400 mg a day.

2. If you are assigned to have bupropion SR added to the antidepressant you are currently taking, the dose of bupropion SR will be slowly increased as described in 1 above.

3. If you are assigned to have aripiprazole added to the antidepressant you are currently taking, aripiprazole will be started at 2 mg a day for the first week and then slowly increased over the next few weeks up to a maximum dose of 15 mg a day. The dose of aripiprazole can be lowered or stopped at any time.

No matter which of the medications you are assigned to take, your study doctor will check to see how your depression symptoms are changing and may increase or decrease the dose depending on how the medication is working for you and whether you experience any side effects. Once you are on a steady dose of medication, your study doctor will check you at each study visit for side effects. Treatment will be available to you for any side effects that bother you.

If you reveal to us thoughts, intentions, or plans to harm yourself (or others), the study team must take action to ensure your safety (and the safety of others). This may include, but is not limited to, evaluation in the psychiatric emergency room and/or hospitalization.

The schedule for the first seven visits at the medical center will be as follows no matter which treatment you are on:

- **Week 1**: Scheduled one week after you are enrolled, to check your progress and increase the dose of the study medication if you are tolerating it well.
- **Week 2**: Scheduled two weeks after you are enrolled, to check your progress and increase the dose of the study medication if you are tolerating it.
- **Every two weeks between week 2 and week 12 (i.e., weeks 4, 6, 8, 10 and 12)**: Your progress on the medication(s) will be checked at every visit. Doses of medication(s) may be increased or decreased based on your response and any side effects you may be experiencing.
If you improve enough to continue past week 12, the schedule will be as follows:

- Every four weeks until you have been in the study for 9 months (weeks 16, 20, 24, 28, 32 and 36):

At the beginning of the study and again after 3, 6, and 9 months, the study staff will ask you to answer questions that may take between 60 and 90 minutes. In addition, at each visit you will be asked to complete several short questionnaires, taking about 30 minutes to complete, focusing on symptoms of depression and possible side effects. We will also gather information on the VA health care that you receive and its cost from your VA medical record and other VA databases. These databases have information on your health care at all VA facilities nationwide. We will ask you to report what medical care you have received outside of the VA. This will not affect your care at the VA or any benefits you might be receiving.

When the study ends, your personal clinician will be alerted through a note in your electronic medical record. You will be given a 30 day supply of your study medication and asked to make a follow-up appointment with your personal clinician for continuing treatment.

After beginning the study, if you decide you do not wish to continue, it is very important for your safety that you tell your study doctor or other members of the study staff. The study team will then make sure your personal clinician takes over your care.

While you participate in this study, it is important that you inform the study staff if you begin to take a new medication not related to this study. This is important to avoid any problems because sometimes medications should not be combined. It is also important to inform the study staff if you develop another medical or mental health problem that needs treatment either inside or outside the VA and of any other important changes in your health or healthcare.

If you participate in this study, you will be asked to:

- Take the study medications as prescribed by your study doctor;
- Come back to the medical center after one week so your medications can be checked, then come back every 2 weeks for 12 weeks and every 4 weeks for up to 9 months;
- Keep your study appointments. If you must miss an appointment, contact a member of the study team to reschedule as soon as possible;
- Have blood drawn a minimum of every 12 weeks and more frequently if indicated by side effects;
- Have urine collected before you are enrolled in the study to check for pregnancy on all females of child-bearing age;
- Complete evaluations of your symptoms of depression, quality of life, general well-being, and any side effects;
- Immediately notify a member of the study team if you suspect you may be pregnant;
- Keep the study medication in a safe place away from children and for your use only;
- Ask questions as you think of them;
- Tell the investigator or research staff if you change your mind about staying in the study;
- Not take part in any other research project without approval from the investigators. This is to protect you from possible injury from things such as extra blood drawing or potential drug interactions. Taking part in other research studies without first discussing it with the investigators of this study may invalidate the results of this research, as well as that of the other studies.
- Not start any new psychotherapy regimen except for couples therapy, occupational, or supportive therapy, or general counseling.

The people you will be in contact with in this study are a study doctor, a study coordinator, and a study evaluator who will be assigned to ask you questions about your symptoms of depression or ask you to complete questionnaires about your depression. Visits will be done in examination rooms or other private settings.

Some studies have shown that for some types of depression, depression-specific psychotherapy is as effective as medication alone, and that the combination of psychotherapy with medications may be better than either a single medication or psychotherapy alone. You may enroll in this study if you are already receiving psychotherapy. However, you will be asked not to start any new depression-specific psychotherapy treatment while in the study. If you do start new psychotherapy during the study, you will be withdrawn from the study and referred back to your personal clinician to continue treatment for depression. You may attend general counseling, couples therapy, occupational therapy, or supportive therapy and still participate in this study. Psychotherapy treatment is not part of this study.

Pregnant women may not enroll in this study. Pregnancy tests will be conducted before enrollment for all women who could become pregnant. The Department of Veterans Affairs will
pay for the pregnancy test. If you are a woman of child-bearing age, you are advised to use birth control methods to avoid becoming pregnant during the time you are on the study medication. Birth control methods might include birth control pills, a diaphragm, an intrauterine device (IUD), foam or jelly that makes sperm inactive, condom use, or other methods recommended by your health care provider.

You should promptly notify the researchers if you suspect you may be pregnant (e.g., missed or late menstrual period). If you become pregnant, you will be discontinued from the study and referred to your healthcare provider for follow-up. This provider will be informed of your participation in the study.

POSSIBLE RISKS OR DISCOMFORTS

Any medication has possible risks and discomforts. The medications in this study may cause all, some or none of the risks or side effects listed. Rare, unknown, or unforeseeable (unanticipated) risks also may occur. Risks of the usual care you receive are not risks of the research and are not included in this consent form. You should talk with your health care providers about risks of usual care.

Each of the treatments in this study has its own risks or possible discomforts. You will need to know about all of these possible risks and discomforts because you will not know which treatment you will receive until agreeing to participate.

The risks of the medications in this study are the same as they would be if you were taking them without being in a study. Many people who take bupropion SR or aripiprazole experience no or minor side effects. The frequency and severity of side effects depends on many factors including dose, duration of therapy, and individual susceptibility. The possible side effects, warnings and cautions associated with bupropion SR and aripiprazole are listed below. This is not an all inclusive list but is representative of items of potential clinical significance. For more information on these medications, you may consult further with the study doctor or refer to a standard text such as the Physicians’ Desk Reference (PDR) or the United States Pharmacopoeia Dispensing Information (USPDI). We will give you a complete copy of the FDA approved patient Medication Guide for these medications for you to keep along with a copy of this consent form.

Bupropion SR: Bupropion SR is available as a brand name medication (Wellbutrin SR®) and as a generic medication from several different companies. We will be using a generic medication in
this study. SR simply means “sustained release.” This tablet was made to be taken twice a day (as compared to three times a day for the regular bupropion).

The most common side effects of bupropion SR and the percent of patients experiencing them are found in the next table.

### Possible side effects with bupropion SR

<table>
<thead>
<tr>
<th>Category</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common (20-30%)</td>
<td>Headache, dry mouth</td>
</tr>
<tr>
<td>Common (10-20%)</td>
<td>Weight loss, nausea, trouble sleeping, dizziness, sore throat</td>
</tr>
<tr>
<td>Less common (5-10%)</td>
<td>Decreased appetite, constipation, diarrhea, infection, shakiness, ringing in the ears, urinating more often, stomach pain, agitation, anxiety, fast heartbeat, muscle pain, skin rash, sweating</td>
</tr>
<tr>
<td>Uncommon (1-5%)</td>
<td>High blood pressure</td>
</tr>
<tr>
<td>Rare (less than 1%)</td>
<td>Seizures, increased thoughts of hurting yourself</td>
</tr>
</tbody>
</table>

Some patients have thoughts of hurting or killing themselves when they first start taking bupropion SR or other antidepressant medication. Any worsening of your depression or thoughts of hurting yourself should be reported to your study doctor right away.

High blood pressure (hypertension): While taking bupropion SR, some people (2.5% or about 2 to 3 out of every 100 patients) get high blood pressure that is almost always mild but can rarely be severe. The chance of high blood pressure may be higher if you also use nicotine replacement therapy (such as a nicotine patch) to help you stop smoking.

Seizures: There is a small chance, 0.4 % (4 in 1000) or less of having a seizure (sometimes called a convulsion or fit) with bupropion SR, especially in people with certain medical conditions or who are taking certain medications. Tell your study doctor about all of your medical conditions and do not take any other medications while you are using bupropion SR unless your study doctor has said it is okay. The chance of having a seizure is rare but has been shown to increase with higher doses of bupropion SR. If you have a seizure while taking bupropion SR, stop taking the tablets and seek emergency medical treatment. Contact your study doctor as soon as possible to report the seizure.

**Aripiprazole:** Aripiprazole is a medication approved by the FDA to treat schizophrenia, bipolar disorder (manic-depression), irritability in children with autism, and as add-on treatment to antidepressant medication for major depression. In this study it is being used as an add-on treatment for major depression.

The most common side effects of Aripiprazole (Abilify®) and the percent of patients experiencing them are found in the following table.
### Possible side effects with aripiprazole

<table>
<thead>
<tr>
<th>Category</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most common (20-30%)</strong></td>
<td>Restless feeling or need to move (akathisia)</td>
</tr>
<tr>
<td><strong>Common (10-20%)</strong></td>
<td>Nausea, vomiting, Headaches, blurred vision, constipation, upper respiratory tract infection, dizziness, fatigue, sleepiness, shakiness, muscle stiffness and tremors (extrapyramidal syndrome [or EPS]) which go away after you stop taking aripiprazole</td>
</tr>
<tr>
<td><strong>Less common (5-10%)</strong></td>
<td>High fever and very stiff muscles (neuroleptic malignant syndrome), high blood sugar, drops in blood pressure when you stand up suddenly, low white blood cell count, muscle movements you cannot control (Tardive Dyskinesia [or TD]) which might be permanent, thoughts of hurting yourself</td>
</tr>
<tr>
<td><strong>Uncommon (1-5%)</strong></td>
<td>Weight gain, trouble sleeping</td>
</tr>
<tr>
<td><strong>Rare (less than 1%)</strong></td>
<td>Urinary tract infection, cough, fever, weight gain, dizziness</td>
</tr>
</tbody>
</table>

Aripiprazole may also have more serious side effects, including odd muscle movements. In one short 6 week study of depression, one type of odd muscle movement (often called EPS or extrapyramidal syndrome) was reported by 8% (8 in 100) of patients taking aripiprazole added on to an antidepressant compared to 5% (5 in 100) of patients taking a placebo (sugar pill) added to an antidepressant. This type of involuntary movement goes away after aripiprazole is stopped.

Severe side effects, although rare, may be seen in patients taking aripiprazole or other medications like it. These have been seen mostly in patients taking a high dose of aripiprazole or using the medication for a long time. So far these effects have not been reported in patients taking aripiprazole added to an antidepressant so we do not know if there is any risk to you or how much risk there may be. Just to be safe, you will be watched closely for any of the signs and symptoms related to these severe effects:

- **Neuroleptic Malignant Syndrome (NMS):** A very rare disorder that can lead to death. The symptoms include a high fever and very stiff muscles.

- **High blood sugar (hyperglycemia) and diabetes:** Some patients taking medications like aripiprazole for schizophrenia have had high blood sugar that needed treatment, and some have developed diabetes that did not go away and required treatment with daily medication.

- **Orthostatic Hypotension:** A condition where a large decrease in blood pressure occurs when standing up too quickly from sitting or lying down. This change can cause dizziness and falls. Because aripiprazole has not been studied in many patients with recent heart attack, unstable heart disease, or other serious medical conditions, you...
should let your study doctor know if you have a history of heart attack, other heart
disease, stroke, or high or low blood pressure.

- Low white blood cell count: White cells are important for preventing and fighting
  infections.

- Tardive dyskinesia (TD): Movements you cannot control. These may not go away after
  you stop taking aripiprazole.

- Some patients, especially people less than 24 years old have thoughts of hurting or
  killing themselves when they first start taking aripiprazole. This is not common but
  worsening of your depression or thoughts of hurting yourself should be reported to your
  study doctor right away.

There are also several general precautions you should take while taking aripiprazole:

- Aripiprazole may affect your body’s ability to cool down with strenuous exercise or
  extreme heat. You should take caution when exercising, and talk to your study doctor
  before you start an exercise program.

- You should use special caution when driving or using machinery since the study
  medication may have the potential to impair judgment, thinking, or motor skills.

- Because difficulty in swallowing and aspiration (accidental inhalation of food) has been
  associated with medications like aripiprazole and including aripiprazole, let your study
  doctor know of any changes in your ability to swallow.

No matter which of the three treatments you are assigned to if you are having problems with the
medication, the dose can be decreased or, if necessary, medications can be stopped or you can
be switched to a different antidepressant. If you must stop a study medication because the study
treatment is not helping with your depression, you will leave the study and will be referred back
to your personal clinician to continue treatment for depression. Your study doctor will continue
to provide clinical treatment for your depression for up to 3 months until you are able to resume
treatment with your personal clinician.

If you decide to stop taking the study medication, please inform the study doctor before you
stop. Your study doctor will need to connect you with your personal clinician because s/he may
recommend stopping your study medication slowly to avoid withdrawal symptoms, though this
may not be necessary in all situations. Even if you are switching to another medication, your
study doctor or your personal clinician may still recommend stopping the study medication slowly.

If at any time you experience any thoughts of harming yourself, a trained counselor can be reached 24 hours/day, 7 days/week by calling the VA Veterans Crisis Line at 1-800-273-TALK (8255). You, your family and/or friends can access Veterans Chat and other resources through the National Suicide Prevention Lifeline website: http://www.suicidepreventionlifeline.org.

**Blood tests:** During a blood draw, you may experience some momentary discomfort, bruising, bleeding or pain at the site of needle entry into the vein as you might during any blood draw. There is a very small risk of fainting. There is also a very small risk that infection could occur at the place where the needle goes into the arm. However, we will take all available precautions to prevent an infection by using sterile technique.

**Other risks or discomfort:** It is possible that your depression symptoms may become worse while you are participating in the study. Also, answering questions about your depression symptoms and medical and military history may cause you to feel stressed.

**POTENTIAL BENEFITS**
There may be no benefits to you for taking part in this research study.

Possible benefits may include improvement in your symptoms of depression. The information we get from this study may also help us treat other patients with major depression (or major depressive disorder) in the future.

**ALTERNATIVES TO PARTICIPATING IN THIS RESEARCH**
You may choose not to participate in this study. If this is your decision, you may speak with your personal clinician about the medications offered in this study or alternative medications for symptoms of depression. All of the medications being used in this study have been approved for use in treating symptoms of depression with specific instructions. They would be available to your personal clinician to consider prescribing for you depending on your symptoms and past treatment. Psychotherapy is another option for treating depression.

You may discuss these options with your study doctor and/or personal clinician.

**CONFIDENTIALITY**
During this research study, some of your personal information, including health information, will be collected by study staff and used for the scientific goals of the study. The information that will be collected will include your name, address, telephone number, and social security
number. We will also ask you to provide the name of someone we can contact if we are not able to contact you for follow-up visits. This personal information will not be used to obtain information about you or your health records outside the VA system without your permission. All data collected as part of this study will be protected in the following ways: All research data will be stored on password-protected computers or in locked file cabinets and only approved research staff will have access to this data.

The West Haven VA Cooperative Studies Program Coordinating Center will be the statistical and data coordinating center for this study. The Albuquerque VA Cooperative Studies Program Research Pharmacy Coordinating Center (PCC) will be the central study pharmacy center for the study. The PCC, study pharmacist and the Cooperative Studies Program Site Monitoring, Auditing and Resource Team (SMART) will access your VA medical record using your social security number to monitor your safety during the study. This study involves 35 VA facilities nationwide; however, your data will not be shared across these facilities.

Information related to any serious adverse experiences occurring for persons receiving aripiprazole will be shared with Bristol Myers Squibb (BMS), the manufacturer of the drug and supplier of the drug aripiprazole to the study. This information will be provided in the form of data summaries or individual reports of events that will not identify any participant personally.

When your information is combined with other peoples’ information in the study, your personal information cannot be identified. We will write about the combined data we have gathered. Any talks or papers about this study will not include any information that could identify you.

The information collected for this study will be kept confidential. We will not share your study records or identify you except as described in this informed consent document. There are times when we might have to show your records to other people. For example, someone from the Office for Human Research Protections, the Government Accountability Office, the Food and Drug Administration, the Office of the Inspector General, the VA Office of Research Oversight, the VA Central IRB, our local Research and Development Committee, and other study monitors may look at or copy portions of records that identify you.

We have obtained a Certificate of Confidentiality from the Federal Government. This helps protect your privacy by allowing us to refuse to release your name or other information outside of the research study, even by a court order. The Certificate of Confidentiality will not be used to prevent disclosures to local authorities of child abuse and neglect, or harm to self or others.
The Certificate does not prevent you or a member of your family from releasing data about yourself or your involvement in this study.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. You can search this website at any time. At most, the website will include a summary of the results of the study. The purpose of this database is to allow everyone to see information about clinical trials that are being done or have been done, including all VA sponsored clinical trials. You may view the database and search for this study as “CSP 576” or “NCT01421342”.

COSTS TO PARTICIPANTS AND PAYMENT
Costs to Participants:

You will not be charged for any treatments or procedures that are part of this study. For Veterans who are required to pay co-payments for medical care and services provided by VA, these co-payments will continue to apply for medical care and services provided by VA that are not part of this study. If you are randomized to a treatment that includes the anti-depressant you are currently taking, you will also continue to be responsible for co-payments for that medication. There may be costs associated with transportation to your healthcare facility or time away from work that will not be covered by your participation in this study.

Payment Offered for Participation:

You will receive payment for taking part in this study in order to compensate you for your time and travel. You will be paid $50 for the first research clinic visit when you enroll in the study and $25 for each scheduled follow-up clinic visit that you complete. Thus, if you complete thirteen clinic visits, you will receive a total of $375. You will be paid within a reasonable time after each clinic visit you complete. There will be no reimbursement if you do not come in to the study clinic to complete the interviews. Payment will be issued payment by check, by cash through the Agent Cashier or by electronic transfer of funds according to local medical center procedures. An Internal Revenue Service (IRS) Form 1099, which documents that you received income, will be generated using your Social Security Number.

MEDICAL TREATMENT AND COMPENSATION FOR INJURY

Every reasonable safety measure will be used to protect your well-being. If you are injured as a result of taking part in this study, the VA will provide necessary medical treatment at no cost to you. Financial compensation is not available for such things as lost wages, disability or discomfort due to an injury.
If you should have a medical concern or get hurt or sick as a result of taking part in this study, call:

DURING THE DAY:
Dr./Mr./Ms. __________________________ at __________________________ and

AFTER HOURS:
Dr. /Mr./Ms. __________________________ at __________________________.

Emergency and ongoing medical treatment will be provided as needed.

You do not give up any of your legal rights and you do not release the VA from any liability by signing this form.

PARTICIPATION IS VOLUNTARY
It is up to you to decide whether or not to take part in this study. If you decide to take part, you may still withdraw at any time. If you do not wish to be in this study or leave the study early, you will not lose any benefits to which you are entitled. If you don’t take part, you can still receive all usual care that is available to you. Your decision not to take part in the study will not affect the relationship you have with your doctor, personal clinician, or other staff, and it will not affect the usual care that you receive as a patient.

You are giving us permission to use your personal health information until the goals of this study have been met. You do have the right at any time to take back your permission to use your personal health information for research purposes. However, if your information has already been combined with other peoples’ information in the study, such as when numbers are averaged, or if it has been sent to the Cooperative Studies Program data center, they will continue to use it but no further information about you will be used.

In order to take back your permission for use of your personal information, you must contact your study doctor. If you take back your permission or do not give your permission, you will still receive all the VA medical care and benefits for which you are otherwise eligible, but you will be unable to continue in this research study.

If you decide to withdraw early, you will be referred back to your personal clinician.

RIGHT OF INVESTIGATOR TO TERMINATE PARTICIPATION
The investigator reserves the right to terminate your participation if, in the judgment of the investigator, your continued participation represents a potential for harm. Reasons that the investigator may terminate your participation are:
- It is determined that you are a potential danger to yourself or others;
- Your symptoms of depression are worsening instead of getting better;
- Your treatment for depression has been changed to a different medication or therapy that is not a part of this study;
- You have missed clinic visits or the study team has been unable to contact you; or
- It is determined that you did not meet all study criteria and were entered into the study in error.
- You present with unexpected and serious health events unrelated to the study, such that continued study participation would pose undue risk of continued health problems.

If the study doctor decides to terminate your participation, you will be referred back to your personal clinician.

A group of outside experts (a Data Monitoring Committee) will review this trial on an ongoing basis for safety and effectiveness, and may make recommendations to the VA Cooperative Studies Program to change or stop the study. The VA Cooperative Studies Program, as the sponsor of the trial, may also stop the study at any time.

PERSONS TO CONTACT ABOUT THIS STUDY
If you have questions about your rights as a study participant or you want to make sure this is a valid VA study, you may contact the VA Central Institutional Review Board (IRB). This is the Board that is responsible for overseeing the safety of human participants in this study. You may call the VA Central IRB toll free at 1-877-254-3130 if you have questions, complaints or concerns about the study or if you would like to obtain information or offer input.

SUICIDE PREVENTION NUMBERS:
- VA Veteran’s Crisis Line: 1-800-273-TALK (8255)
- Local Suicide Prevention Contact Information: ________________

SIGNIFICANT NEW FINDINGS
Sometimes during the course of a research study, new information becomes available about the treatment that is being studied that might change a person’s decision to stay in the study. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw from the study, your study doctor will arrange for your medical care to continue with your personal clinician. If you decide to continue in the study, you might be asked to sign an updated informed consent form. Your study doctor could
also decide it to be in your best interests to withdraw you from the study. If so, he or she will explain the reasons and arrange for your usual medical care to continue.

AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

Dr. _______________________________ or someone from the research team has explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. You have been given the chance to ask questions and obtain answers.

You voluntarily consent to participate in this study. You also confirm that you have read this consent, or it has been read to you. You will receive a copy of this consent after you sign it. A copy of this signed consent will also be put in your medical record.

| I agree to participate in this research study as has been explained in this document. |
|---------------------------------------------|-----------------------------|----------------|
| Participant’s Name | Participant’s Signature | Date |
| Name of person obtaining consent | Signature of person obtaining consent | Date |