VA COOPERATIVE STUDY # 590

DOUBLE-BLIND PLACEBO-CONTROLLED STUDY OF LITHIUM FOR PREVENTING REPEATED SUICIDAL SELF-DIRECTED VIOLENCE IN PATIENTS WITH DEPRESSION OR BIPOLAR DISORDER

STUDY CHAIR:	Ira R. Katz, MD, PhD
STUDY DIRECTOR:	Matthew H. Liang, MD, MPH
BIOSTATISTICIANS:	Robert Lew PhD Gheorghe Doros, MA, MS, PhD
STUDY PHARMACIST:	Robert J. Ringer, Pharm.D.
PROJECT MANAGER:	Melynn Nuite, RN, BS, CCRC

PRIVILEGED AND CONFIDENTIAL

Not for distribution beyond the intended function

Table of Contents

EXECUTIVE SUMMARY

Objective: To test the hypothesis that lithium augmentation of enhanced usual care will reduce the rate of repeated episodes of suicidal self-directed violence (repeated suicide attempts, interrupted attempts, hospitalizations specifically to prevent suicide, and deaths from suicide) in participants with bipolar disorder or depression who have survived a recent self-directed violence event.

Background: The hypothesis that lithium can prevent suicide in patients with bipolar disorder and depression is based on data from observational studies and randomized clinical trials conducted to evaluate other outcomes. The question about the effectiveness of lithium for suicide prevention is one of major scientific, clinical, and public health significance. There have been no adequately powered clinical trials conducted specifically to evaluate suicide behaviors as an outcome. Two recent randomized clinical trials failed to recruit adequate numbers of subjects to be conclusive.

The VHA, as the largest national healthcare system with an established program for identifying new suicide attempts, evaluating patients for underlying mental health and medical conditions, providing needed services, connecting Veterans to state-of-the-art suicide risk management, and monitoring outcomes is uniquely able to conduct a large scale clinical trial of lithium for suicide prevention.

The rationale for the study is based on the following:

- Data from observational studies and double-blind randomized clinical trials suggest that lithium can prevent suicide-related behaviors in patients with bipolar disorder and major depression.
- The high risk of suicide in veterans receiving health care services from VHA has persisted despite extensive improvements in mental health services and in programs for suicide prevention.
- Each month, there are over 1,000 unique VHA patients with bipolar disorder or depression who attempt suicide and survive.
- Surviving a suicide attempt is the most powerful known risk factor for death from suicide in VA and elsewhere.
- Approximately 15% of VA survivors reattempt or die from suicide within one year.
- Evaluating rates of reattempts in those who have survived attempts is an established and effective method for testing interventions that may prevent suicide.
- Experimental treatment in CSP-590 supplements usual care for major depression or bipolar disorder.
- Study monitoring and procedures for the management of suicide risk would meet or exceed VA standards and requirements.

- Study procedures optimize the safety of lithium, including the potential risk of overdoses, and meet or exceed all published practice standards. The trial will utilize multiple strategies to minimize risks including frequent monitoring and assessment, determination of lithium levels during titration and at steady state, and dispensing medications in limited quantities in blister packs.
- Our survey of VA psychiatrists indicates that the question is clinically important and compelling and that a clinical trial that demonstrated the hypothesized effect would transform the clinical management of suicidality.

Design: Randomized, double-blind, placebo-controlled clinical trial of lithium versus placebo augmentation of enhanced usual care.

Patient population: VHA patients with bipolar disorder or depression who have survived a recent episode of suicidal self-directed violence.

Primary outcome: Time to the first repeated episode of suicidal self-directed violence, including suicide attempts, interrupted attempts, hospitalizations specifically to prevent suicide, and deaths from suicide

Duration: Total study duration will be 4.5 years. Recruitment will occur over 3 years. Participants will be followed for one year.

Sample size calculations and number of sites required: The design of the study is based on testing for a 37% reduction in the rate of repeated suicidal self-directed violence, a figure based on an effect size of approximately 43% observed in recent studies and then allowing for attenuation due to non-adherence. Adjusting for potential data loss due to attrition, 90% statistical power to detect a significant 37% reduction in reattempt rates at 5% overall type I error would require 1862 subjects. With recruitment of 20% of eligible subjects over a three year period, this would require approximately 9310 potentially eligible subjects. Based on current VA suicide surveillance data, this could be achieved with 29 sites.

ABBREVIATIONS AND DEFINITIONS

CDC	Centers for Disease Control and Prevention
CRF	Case Report Form
CSP	Cooperative Studies Program
CSPCC	Cooperative Studies Program Coordinating Center
CSPCRPCC	Cooperative Studies Program Clinical Research Pharmacy Coordinating Center
DMC	Data Monitoring Committee
DTHP	Drug Treatment and Handling Procedures
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
MAVERIC	Massachusetts Veterans Epidemiology Research and Information Center
MHP	Mental Health Provider
POC	Point of Care
SAE	Serious Adverse Event
SMART	Site Monitoring Auditing and Resource Team
SPAN	Suicide Prevention and Application Network
SPC	Suicide Prevention Coordinator

GLOSSARY OF TERMS FOR KEY PERSONNEL

Study Chair	Principal Investigator, blinded
Study Director	Blinded and directs CSP Coordinating Center component of CSP 590
Central Psychiatrist /Safety Officer	Blinded clinician independent of Study Chair's Office and study sites. With Study Director, directs overall safety program with consultants in clinical pharmacology, nephrology, and cardiology
Study Nephrologist /Safety Officer	Blinded clinician independent of Study Chair's Office who consult on renal function monitoring and individual participants
Study Cardiologist /Safety Officer	Blinded clinician independent of Study Chair's Office who will review EKGs from sites and consult on QTc monitoring on an as-needed basis
Site Investigator	MD or PhD investigator responsible for overall study at individual site
Site Coordinator	Research Team member who organizes study and personnel to carry out the protocol at each site
Site Physician	Research Team member who prescribes study medication
Research Team	The Site Investigator, Site Coordinator, and Site Physician at each site
Treating Mental Health Provider	The clinical staff member(s) responsible for the patient's ongoing mental health care not related to the study protocol. For purposes of study introduction this mental health provider individual does not have to be capable of prescribing medication. If a participant's mental health provider can not prescribe, study staff will ensure that a person capable of prescribing is involved, a minimum of 2 months, prior to the warm handoff.

NOMENCLATURE

Historically, suicide research has been hampered by ambiguity in the language used to describe events (Silverman et al., 2007). For precision, this proposal uses technical language based on current CDC nomenclature for suicide-related events when specifying hypotheses, outcomes, and inclusion criteria (Crosby et al., 2011; see section V of this proposal). When describing findings from previous research, it uses the language of those studies. In other contexts, it uses common language.

I. INTRODUCTION AND BACKGROUND

Suicide and suicide attempts are persistent and growing public health problems for America and for Veterans. There are few evidence-based approaches for their prevention; and, given the importance of the problem, there have been relatively few randomized clinical trials of potential treatments (Dolgin, 2012).

According to estimates from the Centers for Disease Control and Prevention (CDC) (Karch et al., 2006), Veterans account for approximately 22% of the deaths from suicide in the United States (Bossarte, 2013). Applying these proportions to the 36,900 suicides that occurred in the United States in 2009 and the 38,600 that occurred in 2010 leads to estimates that 18 to 22 Veterans die from suicide each day.

It is not clear whether suicide rates in the entire population of Veterans are higher than the overall US population after controlling for relevant variables (Gibbons et al., 2012; Kaplan et al., 2007, 2012; Miller et al., 2009, 2012). In 2006, rates in OEF/OIF Veterans were similar to those of other Americans after controlling for age, sex, and race, but in 2007 they were higher (Kang & Bullman, 2008; Kang, 2012). Whether this trend will continue or will be a time-limited increase similar to that observed after Veterans returned from Vietnam (Wantanabe & Kang, 1996) is not clear.

Whether or not all Veterans are at increased risk, suicide rates are substantially increased among those who use VHA health care services. Information from the Office of Mental Health Operations on causes of death for all Veterans who use VHA healthcare services since 2000 demonstrates that rates among users are higher than those of the general population (McCarthy et al., 2009; Katz et al., 2012). Rates of suicide among users of VHA services are approximately 36 per 100,000 patient years, 38 per 100,000 among men, and 15 per 100,000 among women (McCarthy et al., 2009, *VA MH Operations to Under Secretary*, 2011). Among the deaths from suicide, approximately half have had a mental health diagnosis in the year prior to their deaths; in those with a mental health diagnosis the rate of suicide is 70 per 100,000 (Ilgen, et al., 2010). The highest rates are 113 per 100,000 patient years among Veterans with bipolar disorder where suicide accounts for approximately 110 deaths per year. The highest numbers of deaths among those with mental health conditions are for those with depression where rates are 82 per 100,000 and there are approximately 400 suicides per year. Altogether, diagnosed affective disorders account for about 500 deaths from suicide each year in VHA, or about 25-30% of all suicides among VHA patients.

Since 2008, the Office of Suicide Prevention has maintained a registry of VHA suicide attempts and deaths reported by the Suicide Prevention Coordinators (SPCs) in each Medical Center. This active surveillance registry, VA-Suicide Prevention and Application Network (SPAN), was established to coordinate the identification and reporting of suicide-related events within and across facilities, to facilitate the identification of individuals at high risk to target interventions, and to support both program planning and evaluation. It has served as an important resource for planning the proposed study. Between April 1, 2010 and March 30, 2012, SPCs reported suicide attempts or deaths from suicide that became known to the facility in almost 30,000 Veterans utilizing VA services. Of these, 94% had a primary or secondary diagnosis of depression or bipolar disease documented in their medical records before the attempt or during the evaluation

of the attempt, and approximately half were first time attempters. Of these Veterans, 0.06% died within one week. Among those who survived, 15% reattempted suicide within a year, and approximately 3-5% died from natural or unnatural causes within one year. Suicide attempt survivors have a very high risk for repeated attempts and death.

Current VA Management of Suicidality

The VA's activities in suicide prevention constitute a comprehensive program that includes public health activities, ready access to high-quality health and mental health care services, and interventions targeting individuals at high risk. For those at risk, the program requires supplementing evidence-based treatment for underlying mental health conditions with interventions that directly address the risk of suicide. Documents defining the program are included as Appendix A.

The VA standard of care for the prevention-focused care of patients at high risk is specified in "Patients at High-Risk for Suicide," from the Principal Deputy Under Secretary for Health and the Deputy Under Secretary for Health for Operations and Management, April 24, 2008. This memo requires the Suicide Prevention Coordinator (SPC) at each facility to maintain a list of patients at high-risk for suicide, including, but not limited to those who have survived a suicide attempt. It includes specific language outlining requirements for the care for those at high-risk:

1. Patients at high-risk for suicide must be placed on the high risk list for at least 3 months after discharge. They must be evaluated at least weekly during the first 30 days after discharge.

2. Other patients surviving a suicide attempt and those placed on the high-risk list for other reasons should be evaluated at least weekly for at least the next month.

3. When a Veteran attempts suicide or is identified as being at high risk and placed on the facility's high risk list, the SPC will make personal contact with the Veteran, establish a US mail contact, and contact the Veteran's primary care and mental health provider to ensure that:

   a. The Veteran's mental health diagnoses and care plan have been reviewed in light of the risk of suicide and that the care plan appropriately addresses the Veteran's conditions and functional limitations.

   b. Specific treatments with the potential for reducing suicide risk have been considered. These include clozapine for schizophrenia and lithium for bipolar disorder.

   c. The plan includes ongoing monitoring for suicidality and plans for addressing periods of increased risk. These plans must include specific processes of follow-up for missed appointments.

   d. There is an individualized discussion about means reduction that should address issues such as medication storage, gun safety, and high-risk behaviors.

e. A family member or friend has been identified, either to be involved in care or to be contacted, if necessary.

f. There is a safety plan in the medical record and the Veteran has a copy of the plan.

(1) The plan should be specific and behaviorally oriented. It should be designed to help the Veteran identify times when he or she is at increased risk, and to act to preserve his or her life. It should list situations, stressors, thoughts, feeling, behaviors, and symptoms that suggest periods of increased risk, and step-by-step descriptions of coping strategies and help-seeking behaviors that can be used at these times.

(2) The plan is developed by the Veteran with guidance and support from his or her provider or from the SPC.

(3) The safety plan must include directions for the Veteran about how to get help 24/7, including local VA numbers available and the National Crisis number (1-800-273-TALK).

(4) Periodic review of the plan and discussion of its use in times of stress should be included in the Veterans ongoing care.

A memorandum "Safety Plans for High Risk Veterans" from the Under Secretary for Health to the VISN Directors (July 13, 2010) provided additional information about safety planning. Specifically, it stated that safety plans should:

1. Be developed with participation of patients/families
2. Be provided to patients
3. Include five elements:
    a. Identification of the warning signs that precede a crisis
    b. Identification of internal coping strategies
    c. Indication of when to contact family/others for support or to help resolve a crisis
    d. Identification of when professional agencies should be contacted
    e. Provision of ways to get help, including the phone number for the Veterans Crisis Line
4. Be completed in a timely manner, prior to a Veteran being discharged from an inpatient facility or at the next scheduled appointment for Veterans followed as outpatients
5. Be the focus of the required weekly follow-up visits

Other policies and guidance were specified in VHA Directive 2008-036, "Use of Patient Record Flags to Identify Patients at High Risk for Suicide" released on July 18, 2008, and a memorandum "Standardized Suicide Nomenclature (Self Directed Violence Classification System)" from the Deputy Under Secretary for Health Operations and Management to the VISN Directors on April 19, 2010.

The policy requirements reviewed here were supplemented by the Suicide Prevention Coordinator Orientation Manual issued in August, 2009 and updated July, 2011.

VA provides an array of services that complement the clinical programs specified in these documents. These include the national telephone Crisis Line, 800-273-TALK, the text messaging and internet chat services linked with it, and firearm safety programs required at each Medical Center. There are also ongoing demonstration and research programs for ensuring follow-up and continuity of care for those who come to emergency departments for problems related to suicide, but for whom hospital admission is not necessary.

Focused clinical interventions that may be available in certain facilities include three specific psychotherapies: Cognitive Therapy for Suicide Prevention (Brown et al., 2005), an evidence-based psychotherapy found to be effective for suicide prevention across mental health conditions; Dialectical Behavioral Psychotherapy (Linehan et al., 2006), an evidence-based suicide prevention program for patients with borderline personality disorder and related conditions; and Collaborative Assessment and Management of Suicidality (CAMS) (Ellis, et al. 2012), a promising behaviorally oriented psychotherapy. Other ongoing research, within VA and outside, is evaluating motivational interviewing strategies to enhance safety planning. Specific targets for new research include strategies for promoting firearm safety and other ways to delay access to lethal means, and methods for identifying reasons for living that can be used to inform coping strategies.

The April 24, 2008 memorandum that requires providers to "consider" lithium treatment for patients with bipolar disorder at high risk for suicide was based on the available evidence at the time, as reviewed by VA leadership. However, this recommendation was criticized by a Blue Ribbon Panel convened by the Secretary to review VA's suicide prevention program who argued that, in the absence of any direct data from randomized clinical trials designed to evaluate lithium for suicide prevention, it could not be supported by the available evidence (Hoge et al., 2008). These differences reflect the importance of further research in this area. In fact, the conduct of focused research on suicide prevention is consistent with the vision expressed in the April 24, 2008 memorandum, "VHA strongly encourages research, clinical demonstrations, and the development of best-practices in the care of those at high risk. The activities identified here should be the focus for ongoing innovations."

Clinical Pharmacology of Lithium for Suicide Prevention

Lithium is FDA-approved for treating acute mania and preventing recurrent episodes for patients with bipolar disorder. Other uses supported by evidence from controlled clinical trials, but not by FDA approval, include preventing relapses in major depressive disorder and adjunctive therapy for treatment-resistant major depression (Bauer & Dopfmer, 1999; Bauer et al., 2003; Burgess et al., 2001; Fava & Rush, 2006; Nierenberg et al., 2006; Prien et al., 1984).

Even in the absence of randomized clinical trials, the 2003 American Psychiatric Association Practice Guideline for the Assessment and Treatment of Patients with Suicidal Behaviors stated, "There is strong evidence that long-term treatment with lithium salts is associated with major reduction in the risk of both suicide and suicide attempts in patients with bipolar disorder, and there is moderate evidence for similar risk reductions in patients with recurrent major depressive disorder." The Guideline recognized the potential dangers of overdosing on lithium and recommended appropriate clinical management when it was used for suicide prevention. More recently, the 2013 VA-DoD Clinical Practice Guideline for the Assessment and Management of Patients at Risk for Suicide (Department of veterans Affairs, Department of Defense, 2013) stated, "Lithium should be considered for patients diagnosed with bipolar disorder who do not have contraindications to lithium as it has been shown to reduce the increased risk of suicide associated with this illness."

A 2001 Cochrane review of lithium for maintenance treatment for bipolar disorder (Burgess et al., 2001) updated in 2009 found the evidence for lithium to be inconclusive. However it stressed the importance of the issue, saying, "Low suicide rates in lithium-treated patients have led to claims that lithium has a specific anti-suicidal effect. If so, this is of considerable importance as treatments for mental disorders in general have not been shown convincingly to be effective in suicide prevention." This conclusion is echoed in the September 10, 2012 release of the US National Strategy for Suicide Prevention, "… clozapine has been found to be effective in reducing suicidal behaviors among patients with schizophrenia, and lithium shows promise in patients with mood disorders."

The effect sizes reported for observational studies and meta-analyses of lithium for the prevention of suicide and suicide attempts are, in general, large in depression, bipolar disorder, and mixed populations of those with affective disorders (Ahrens et al., 1993, 1995a, 1995b; Baldessarini et al., 1999a, 1999b, 2001, 2003, 2006; Brodersen et al., 2000, 2001; Coppen et al., 1992, 1998, 2000; Dunner, 2004; Goodwin et al., 2003; Guzetta et al., 2007; Hanus & Tuma, 1992; Isometsa et al., 1992; Kallner et al., 2000; Kessing et al., 2005; Modestin et al., 1992; Muller-Oerlinghausen et al., 1991, 1992a, 1992b, 1994, 1996, 2003, 2005; Tondo et al., 1997, 1998, 2000, 2001; Vestergaard & Aagaard, 1991. Key studies are summarized in Table 2). Moreover, observational studies suggest that the preventive effect may be independent of other symptom-related outcomes (Ahrens, 2001; Muller-Oerlinghausen, 2001).

However, some observational studies of lithium for suicide prevention are negative. These include studies on attempt rates from a single psychiatric practice, from a single VA site, and from a pharmaceutical claims database (Collins & McFarland, 2008; Yerevanian et al., 2003, 2007). Secondary analyses from two large observational studies, Collaborative Depression Study and the Systematic Treatment Enhancement Programs for Bipolar Disorder did not demonstrate protective effects from lithium (Coryell et al., 2001; Marangell et al., 2008).

Findings from two recent randomized clinical trials of lithium for managing symptoms of bipolar disorder were negative for suicide-related outcomes. The LITMUS study (Nierenberg et al., 2013) evaluated "optimized personalized therapy" for bipolar disorder with or without moderate doses of lithium in an open-label, flexible-dose randomized clinical trial to determine whether lithium led to improved symptom outcomes. Findings for the primary outcomes, the control of affective symptoms, were largely negative. Other findings included the absence of differences

between groups in the emergence or persistence of suicidal ideation. The publication stated that there were no differences between groups in the frequency of suicide-related behaviors or in the rate of hospitalizations to avoid them; however, no data related to these outcomes were presented. The BALANCE study (2010) evaluated lithium plus valproate versus lithium alone versus valproate alone for the prevention of relapses in patients with bipolar disorder in an open-label randomized clinical trial. For the primary outcome, relapse prevention, lithium plus valproate or lithium alone were more effective than valproate alone. Using the investigators' terminology, the frequency of deliberate self-harm ranged from 2% on lithium alone to 5% on valproate alone, but the study was not powered to test for differences.

In addition, two recent observational studies have reported negative findings in VA patients. In one study, Ahearn and her colleagues (in press) evaluated medical record data on suicide attempts in patients with bipolar disorder at five VA medical centers from 1999 to 2004 and found no significant differences between those taking lithium and valproate as mood stabilizers; however, the number of attempts in patients taking either medication was relatively low, and there was limited power for detecting even moderate to large differences. Important observations were that a majority of VA patients with bipolar disorder were taking a second generation antipsychotic medication, often in combination with lithium, valproate, or other mood stabilizers, and that those taking antipsychotic medications had higher rates for suicide attempts than those taking mood stabilizers alone. There have been significant changes in the usual care for bipolar disorder since the time of the earlier observational studies. In a second recent study, Smith (2012) compared deaths from suicide in patients taking lithium or valproate in a case control study with propensity score matching. The basic finding from the primary analysis was that there were no significant differences between the two agents. However, secondary analyses demonstrated that those who were discontinued from lithium were at greater risk than those who remained on lithium, those who were discontinued from valproate, and those who remained on valproate. (Issues related to discontinuation and withdrawal of lithium are addressed in Sections XII Human Subjects and Informed Consent and XIV Follow-up and Termination).

In reviewing this literature, it is important to recognize that the positive findings from observational studies could, in principle, reflect bias by indication (Bowden & Fawcett, 2004; Johnston, 2001; Yerevanian et al., 2004). Given concerns about the safety of lithium, providers may be less likely to prescribe lithium for those patients perceived as being at higher risk for suicide. To the extent that the providers' perceptions are valid, this could lead to an apparent protective effect for lithium.

The most robust evidence for a lithium effect comes from a 2005 meta-analysis by Cipriani and colleagues of 32 clinical trials with 1389 patients randomized to lithium and 2069 patients randomized to other pharmacological treatments for affective disorders (Cipriani et al., 2005). Because the findings were derived from randomized clinical trials, the results were not subject to bias by indication. The meta-analysis demonstrated significant protective effects for death from suicide (Peto odds ratio=0.26, 95% CI 0.09-0.77) and for both deaths and (non-fatal) attempts (Peto odds ratio =0.21, 95% CI 0.08 to 0.50). These effects, a 74% decrease in deaths from suicide and a 79% decrease in suicide-related behaviors, are comparable to the effect-sizes estimated in the observational studies. Similar findings were reported from a reanalysis of findings from a study of lithium and carbamazepine in preventing recurrences in bipolar disorder that was not included in the Cipriani meta-analysis (Thies-Fletchner et al., 1996).

More recently, Cipriani and colleagues updated and extended their meta-analysis (and included the Lauterbach et al (2008) and the Oquendo et al (2011) studies discussed below). The findings from planned analyses were that lithium was significantly more effective than placebo in reducing the number of suicides (Peto odds ratio= 0.13, 95% CI 0.03-0.66) and deaths from any cause (Peto odds ratio 0.38, 95% CI 0.15-0.95), but not episodes of deliberate self harm (Peto odds ratio =0.60. 95% CI 0.27-1.32). Other findings from planned analyses were that there were no significant differences between lithium and other medications in effects of suicide or deaths from any cause. Lithium was more effective than carbamazepine in reducing the number of deliberate self-harm events (Peto adds ratio 0.14, 95% CI 0.02-0.83), but there was no significant differences for other medications.

There have been two recent randomized clinical trials of lithium for preventing suicide attempts in patients who survived an initial attempt. Both were unable to enroll their target number of participants. As a result, both were inadequately powered and neither was definitive. One study evaluated adjunctive treatment for preventing repeated suicide attempts in depression, but it was terminated prematurely after only 167 of the planned 468 subjects were enrolled. In this study, Lauterbach and colleagues (2008) reported a hazard ratio for lithium of 0.517 that, as expected given the reduced sample size, was not significant (95% CI 0.18-1.43). In the second study, Oquendo and co-investigators (2011) evaluated lithium versus valproate for treatment of bipolar disorder in patients with previous suicide attempts. It reported negative results for the prevention of repeated attempts after 2.5 years for 98 of a planned 232 randomized subjects. Post-hoc sample size calculations showed the study had 80% power for detecting an 85% reduction for lithium relative to valproate. Additional post-hoc calculations by CSP-590 investigators demonstrate that the study would have had only 14.4% power for detecting a 50% effect, and only 9.3% power for a 40% effect. The negative results provide evidence against only a very large effect. The raw data indicate that 16% of the valproate group reattempted over 2.5 years; reattempts for those on lithium were 33% lower at 1 year and 25% lower at the conclusion of the study.

Most recently, the United States Preventive Services Task Force (USPSTF) summarized research in this area in a draft recommendation, “Screening for Suicide Risk in Adolescents, Adults, and Older Adults: US Preventive Services Task Force Recommendation Statement.” It stated, “Minimal data are available on the effectiveness of medications in preventing suicidal behaviors,” and, referring to the Lauterbach study, “The lone study was a short-term fair-quality trial that assessed the use of lithium. The study reported hazard ratios that suggest a possible benefit for lithium, but were not statistically significant. There was a statistically significant lower rate of suicide deaths per patient year in the intervention group; however, the study had high attrition rates and there were only three suicide deaths.” It went on to state, “In the one medication trial that evaluated treatment with lithium, a higher percentage of patients in the treatment group withdrew from the study due to adverse effects compared with the placebo group (13% vs. 2%), though the statistical significance was not reported and the overall dropout rates were similar between the two groups.” (USPSTF, 2013)

Conceptual Models for the Hypothesized Effects of Lithium on Suicide Behaviors

The mechanisms through which lithium controls symptoms and prevents recurrences in bipolar disorder and depression are not completely understood. Even less is known about the

mechanisms that may underlie its putative effect in preventing suicide. One of the strategies used to investigate mechanisms for the treatment of bipolar disorder has been to evaluate actions that are common to both lithium and mood-stabilizing antidepressants. However, this is not applicable for studies related to suicide prevention. First, the effect on suicide prevention is unique to lithium, and, second, it may not be directly related to the effect associated with control of affective symptoms (Ahrens, 2001; Muller-Oerlinghausen, 2001). In the absence of a mechanism of action, it is useful to review the conceptual models that could inform research.

Empirical Models based on Suicidality as a Treatment Target:

This proposal is based on a "target symptom" conceptual model for the use of lithium for suicide prevention that views the risk of suicide as a potential target for treatments to be provided in addition to treatments focused on specific disorders. In this model, the value of defining suicidality as a target follows from observations that it does not uniformly respond to treatments directed toward the underlying affective disorders even when they reduce symptoms. A similar approach underlies clinical use of antipsychotic medications to target delusions when they occur in depression or bipolar disorder (Meyers et al., 2009; Kunzel et al., 2009), and ongoing research on strategies for augmenting treatment with antipsychotic medications with agents that could target the cognitive deficits observed in schizophrenia (Marder, 2011).

Impulsivity and/or Aggression as Mediators:

A number of studies suggest that increased impulsivity, aggression, and other forms of behavioral dyscontrol may occur in patients with mental health conditions, including depression and bipolar disorder, and that they may contribute to the risk of suicide in these conditions (Brodsky et al., 2001; Brent et al., 1994; Dougherty et al., 2004; Grunebaum et al., 2006; Mann, 1999, 2003; McGirr et al., 2009; Oquendo et al., 2004; Perroud et al., 2011; Swann et al., 2005).

The evidence for an effect of lithium on impulsivity and/or aggression is suggestive. Small clinical trials suggest benefits of lithium for aggression in prison populations (Sheard, 1971, 1976) and children with conduct disorders (Campbell et al., 1984, 1995; Malone et al., 2000). However, a meta-analysis identified substantial limitations in the evidence that lithium was effective for managing "impulsive or repetitive aggression" in patients without intellectual disability, organic brain disorder, or psychosis, and determined that the available evidence provided comparable support for certain anticonvulsants as well as lithium (Jones et al., 2011). Other small trials of lithium for impulsivity suggested effectiveness in patients with "emotionally unstable character disorder," (Rifkin et al., 1972) and in those with pathological gambling (Hollander et al., 2005).

A model in which impulsivity and aggression can serve as endophenotypes (deconstructed components of complex behavioral phenotypes) (Gottesman & Gould, 2003; Kovacsics et al., 2009, 2010; Mann et al., 2009; Ohmura et al., 2011; Turecki, 2005) for suicide underlies research on neurobiological mechanisms underlying suicide and the effects of lithium. Aggression and impulsivity can be evaluated in humans and animals; the same behaviors and traits that could serve as mediators in clinical populations could, from a different perspective, support the design of animal research on questions that are fundamentally human.

Although the proposed study is designed to improve suicide prevention and to decrease the public health burden of suicide, a rigorous test of the effectiveness of lithium could also catalyze research to probe mechanisms and to develop alternative agents.

II. SIGNIFICANCE OF THE PROPOSED RESEARCH TO THE VA

Suicide in Veterans is a major public health problem, a source of considerable anguish to families and communities, and a challenge to a health care system that already devotes substantial efforts and resources to solve the problem. The high rate of suicides and suicide attempts has persisted despite every effort to track the problem, enhance awareness and increase access to specialized mental health services and programs for veterans.

Each year, approximately 9,000 VA patients with bipolar disorder or depression who would be eligible for lithium treatment attempt suicide and survive. Based on data from SPAN and the CDC, 15% of those who survive attempts make a reattempt within one year, and approximately 0.5% die from suicide within one year (see below). The rate for reattempts is comparable to estimates from community studies, but the rate of deaths may be somewhat lower in VA (0.5% versus approximately 2%; Owens et al., 2002).

If lithium treatment prevented approximately 40% of repeated attempts in patients with depression or bipolar disorder during the year after an attempt (see Section VII below), it would prevent almost 600 reattempts. If it prevented approximately 40% of deaths, it would save on the order of 20 lives each year. These estimates (and the others included below) are limited to the effects that would occur during one year of preventive treatment; they do not estimate the potential benefits of longer term maintenance treatment. However, the potential effect of lithium could be far larger. As discussed above, there are approximately 500 deaths from suicide each year in VA patients with depression or bipolar disorder. If lithium treatment were utilized in these patients, it could, in principle, lead to approximately 200 fewer deaths from suicide per year.

In considering the impact of lithium treatment, it is important to consider the potential effects on all-cause mortality among those who have survived a suicide attempt. There is substantial literature demonstrating that individuals who have survived a suicide attempt are at increased risk for death, not just from suicide, but from other forms of unnatural, external, or accidental deaths as well (Bergen et al., 2012; Cooper et al., 2005; Hawton et al., 1988, 2003, 2006; Karasouli et al., 2010; Nordentopf et al., 1993; Owens et al., 2002; Ostamo & Lonnqvist, 2001). One possible explanation for this finding may be that medical examiners and coroners may under-diagnose suicide; another is that there may be shared risk factors for suicide attempts and for death from unnatural causes.

In one preliminary investigation in the VA, 2276 patients who attempted suicide in the first quarter of 2009 were identified from the SPAN data set. Based on CDC data, 3.0% died during the subsequent year, 0.44% of the total died from suicide, and 1.30% from other unnatural causes. In another investigation in VA, 39,803 individuals were identified from medical record data as having survived a suicide attempt between 2000 and 2008. Based on CDC data, 14.8% had died by the end of 2009. 4.7% died within one year after their attempt, 0.80% from suicide

and 0.96% from other unnatural causes. For the 8331 Veterans identified from medical records as attempting suicide in 2008, 0.54% died from suicide in 1 year and 0.71% from other unnatural causes.

There are also epidemiological findings demonstrating increased mortality from natural causes among those who have survived suicide attempts (Hawton et al., 1988, 2006; Nordentopf et al., 1993; Ostamo & Lonnqvist, 2001). This could reflect the reaction to a medical diagnosis as a precipitant of suicide (Fang et al., 2012; Johnson et al., 2012). Other explanations include bias against reporting suicide on the part of medical examiners, shared risk factors (e.g., smoking), or non-adherence with medical care as a means for suicide. Regardless, these findings suggest that counts of suicide as a cause of death probably underestimate the total burden in the VA and in the nation.

Translating these findings suggests that if this study were positive and the findings were implemented in the target population, the lives saved could go beyond the number who died from suicide to include a proportion of those who survived attempts who died from other causes.

III. PRELIMINARY RESEARCH

Survey of Potential End-users of the Study: Importance of the Study Question

In preparing this proposal, all VA psychiatrists, the potential users of the study results, were queried about a number of issues. 879 VA psychiatrists (an overall response rate of 31.8%) responded to an online anonymous survey. 93.3% of the responders currently prescribed lithium for patients with bipolar disorder and 72.7% for patients with major depression who did not respond to antidepressants.

Providers were asked to: “Assume your patient:

- Has bipolar disorder or major depression
- Has survived a recent suicide attempt
- Has no contraindications to lithium
- Is first stabilized medically and psychiatrically
- Is receiving clinical care per VA requirements for managing patients at high-risk for suicide.”

Under these assumptions, respondents were asked: “Would you refer such a patient to a randomized, double-blind, placebo-controlled study of adjunctive lithium treatment for suicide prevention? (Lithium will be carefully monitored),” and 74.2% answered “Yes”, 16.8% were unsure, and 8.9% answered “No”.

Finally, psychiatrists were asked “What overall percentage of reduction in suicide attempts would convince you to prescribe lithium for your own patient after a recent attempt?” Options between 10-100% were given in 10% increments. 78.5% of the respondents answered this question. The mean response was 38% and the mode, 50%. Sixty-one percent of the respondents would prescribe lithium if it reduced suicide attempts by at least 40% and eighty-three percent if it reduced attempts by at least 50%. These findings support the effect size used for this trial; and

that the effect size estimated from recent studies used for our sample size calculations would lead a majority of psychiatrists to change their practice to prescribe lithium for appropriate patients with bipolar disorder or depression who survive a suicide attempt.

Overall, the responses demonstrate that respondent VA psychiatrists are experienced in the use of lithium, strongly supportive of the proposed study, and would change their practice if effect sizes we targeted were documented.

IV. STUDY OBJECTIVES and EXPERIMENTAL DESIGN

The proposed study is a double blind, placebo controlled, randomized clinical trial testing the effectiveness of lithium augmentation of enhanced usual care for prevention of repeat episodes of suicidal self-directed violence including suicide attempts, interrupted attempts, hospitalizations for the prevention of suicides, and deaths from suicide, as determined by the Outcomes Adjudication Committee, over a one year period. The study sample will include patients with depression or bipolar disorder, with or without non-psychotic comorbid conditions, who have survived a suicide attempt, experienced an interrupted attempt, or were hospitalized to prevent suicide within six months prior to enrollment.

The primary hypothesis is that lithium is superior to placebo for the prevention of episodes of suicidal self-directed violence over time. The primary outcome measure is time from randomization for treatment allocation to the first episode, either a suicide attempt, an interrupted attempt, a hospitalization specifically to prevent suicide, or death from suicide.

As secondary objectives of the study, the efficacy of lithium will be evaluated for the prevention of subtypes of suicidal self-directed violence, for all suicidal self-directed violence events (even after the first recurrence), for the prevention of repeated events in subgroups as well as the entire sample, and to identify potential mediators.

The tertiary objective of the study is to extend the follow up period using electronically available data to describe patterns of lithium use following active participation in the study participants, as well as to evaluate rates and determinants of suicide reattempts and all cause mortality over a longer follow up period.

The study will enroll and randomize 1,862 patients to receive either lithium or placebo with enhanced usual care. The study is projected to run a total of 4.5 years with 3 years of recruitment, 1 year of follow-up on lithium or placebo, and time for start-up and closeout as indicated in the study budget. We expect to enroll, on average, 65 patients per site at 29 VA medical centers.

V. STUDY POPULATION

Inclusion Criteria

Admission of patients to CSP590 will require that:

1. They have survived an episode of suicidal self-directed violence (including suicide attempts and interrupted attempts; see below) that occurred within six months of initial consent to the study, or they were admitted to a mental health inpatient unit specifically to prevent suicide within six months of initial consent to the study.

2. They have a diagnosis of an affective disorder meeting DSM-IV-TR (2000) criteria for Bipolar I Disorder, Bipolar II Disorder, or current or recurrent Major Depressive Disorder. Meeting the diagnosis for a current Major Depressive Disorder requires the presence of a Major Depressive Episode (see below).

3. They are able and willing to identify one or more family members, friends, or other contacts and give permission for both clinical providers and the Research Team to contact them if the patient cannot be reached.

4. They are able to provide informed consent

5. There is concurrence from the patient's mental health provider about inclusion/exclusion criteria and confirmation of the providers' willingness to work with the research team in managing the patient during the course of the study (see below). The provider responsible for the patient's general medical care has been made aware of the participation

Rationale:

This study will be implemented in FY2015, when the mental health field in VA and the remainder of the United States is transitioning from use of DSM-IV-TR (American Psychiatric Association, 2000) to DSM-5 (American Psychiatric Association, 2013) to guide the diagnosis of mental disorders. To maximize compatibility of research diagnoses with the clinical diagnoses available through VA electronic medical records, inclusion and exclusion criteria for this study will remain based on DSM-IV-TR. However, procedures for diagnosis and assessment of key disorders will be modified, as needed, to allow characterization of patients in terms of both DSM-IV-TR and DSM-5 diagnostic criteria.

For inclusion in this study, suicide attempts must meet the definition for a suicide attempt based on the CDC's document, "Self Directed Violence and Surveillance: Uniform Definitions and Recommended Data Elements" (Crosby et al., 2011). This system was developed in collaboration with VA, and was subsequently adopted by both DoD and VA as a means for defining attempts on the basis of behavior, reports or judgments about intent, and context. According to the CDC definition, an attempt is, "A non-fatal self-directed potentially injurious behavior with any intent to die as a result of the behavior. A suicide attempt may or may not

result in injury." It includes suicidal self directed violence, "Behavior that is self-directed and deliberately results in injury or the potential for injury to oneself. There is evidence, whether implicit or explicit, of suicidal intent." The CDC definition includes interrupted self-directed violence-by self or by other.

"By self" (in some documents, termed "abortive" suicidal behavior) means a person takes steps to injure self but is stopped by self prior to fatal injury," when there is implicit or explicit evidence of suicidal intent. "By other" means a person takes steps to injure self but is stopped by another person prior to fatal injury. The interruption can occur at any point during the act such as after the initial thought or after onset of behavior.

Finally, the inclusion criteria go beyond the CDC definition to include cases where patients were hospitalized to prevent suicide. To summarize, the goal in defining the inclusion criteria related to suicidal self-directed violence is to ensure that they are representative of those clinically considered to have attempted suicide or have been at imminent risk.

The mental health diagnosis used in this study will be based primarily on information from the structured diagnostic assessments conducted during the eligibility evaluation (See Section VI, Table 1 and Table 6). Any apparent discrepancies between these diagnoses and those in the medical record will be resolved by further inquiries to the patient (and, where appropriate, the family) about current and previous symptoms and further discussion with the patient's mental health provider. The Research Team will establish a final diagnosis on the basis of the structured diagnostic assessments, the medical record, and other available data. Inclusion will require a Research Team diagnosis of bipolar disorder or current or recurrent major depression and the absence of exclusionary diagnoses together with the mental health provider's concurrence with the validity of these diagnoses.

Procedures for the diagnosis of a current or recurrent Major Depressive Disorder are designed to identify lifetime diagnoses. For patients for whom the current attempt has occurred within the context of an initial episode of depression, admission will require that the criterion symptoms for a Major Depressive Episode are fully met, either at the time of the interview or when the episode was at its worst. For those with recurrent episodes, admission will require that the criterion symptoms were met at the times of screening, the baseline assessment, or when the current episode was at its worst.

Mental health comorbidities that are not exclusions include PTSD, panic disorder, generalized anxiety disorder, and personality disorders.

A potential concern about inclusion of individuals with personality disorder is that they may exhibit multiple, repeated episodes of suicide attempts or other forms of self-destructive behaviors, and that, in this context, attempts and self-destructive behavior may become less valid as surrogate measures for suicide. This possibility is addressed through the exclusion criterion related to multiple attempts (see below).

A medical record diagnosis of schizoaffective disorder may not be an exclusion when there is also documentation of bipolar disorder. As emphasized in DSM-5 (p. 138), "Schizophrenia, schizoaffective disorder, and delusional disorder are all characterized by periods of psychotic

symptoms that occur in the absence of prominent mood symptoms." Inclusion of patients with chart diagnoses of schizoaffective disorder will require documentation of symptoms and a history consistent with a diagnosis of bipolar disorder, the absence of a history of psychotic symptoms in the absence of prominent mood symptoms, and the judgment of both the Research Team and the patient's mental health provider that the most appropriate diagnosis is bipolar disorder, not schizoaffective disorder.

Participation will also require concurrence from the patient's mental health provider and a notification to the provider responsible for the patient's general medical care. The rationale for this requirement is to ensure that the mental health providers concur with the Research Team's evaluations related to inclusion/exclusion criteria, that they are not aware of additional information not included in the medical record that may affect eligibility, that treatment with study medication is compatible with any planned modifications in treatment, and that the providers are committed to working with the Research Team to manage the patient during the course of the study.

If there is a prescribing mental health provider (MHP) we will require that concurrence is obtained from that mental health provider. However, if there is no prescribing mental health provider involved with the participant at the beginning of the study or if one is lost during the study, a mental health provider who is able to prescribe medications and who is able to assume care of the participant at Month 12/End of Study will be identified. At end of study at a "warm handoff", the mental health provider is un-blinded. With the participant, they can continue or taper off lithium or start lithium (in the event they have been on placebo). The research team ensures that a prescribing mental health provider is involved prior to the warm handoff and that a mental health provider will be identified prior to study Month 10
Notification to the provider responsible for the patient's general medical care alerts the provider to the patient's involvement in the study. In addition, it should acknowledge the presence of any medical conditions or medications that may require additional monitoring during the course of the trial.

Exclusion Criteria

Potential subjects will be excluded if they have:

1. Schizophrenia

2. A history of psychotic symptoms (hallucinations or delusions) in the absence of prominent mood symptoms attributable to Major Depressive or Manic Episodes, delirium, or substance use/withdrawal (see rationale above)

3. Cognitive impairment defined as a Brief Orientation Memory and Concentration Test (Katzman et al., 1983) score > 10

4. Lack of decision-making capacity to evaluate the risks versus the benefits of participation as determined by a score of <14 out of a possible 20 on up to 2 assessments using the Jeste Decision-Making Capacity Assessment – University of California, San Diego Brief

Assessment of Capacity to Consent (UBACC) (Jeste et al., 2007), or adjudication of incompetence and the appointment of a guardian or conservator

5. Six or more previous lifetime suicide attempts as ascertained through SPAN, reports from family, or patient self-report

6. Current or recent (within six months) use of lithium

7. History of significant adverse effects of lithium as ascertained through the medical record or self-report

8. Unstable medical conditions or specific medical comorbidity:

   a. Congestive heart failure by Framingham criteria (McKee et al., 1971)
   b. QTc greater than or equal to 450 ms for men or
      QTc greater than or equal to 460 ms for women (Measurement of the QT interval and the risk associated with QTc interval prolongation: A review. Moss et al.,1993).
   c. Chronic renal disease as defined by national Kidney Foundation Disease Outcome Quality Initiative (KDOQI) criteria (2000) with a estimated GFR less than 60 mL/min/1.73m^2.

9. Any possibility of being pregnant or not on appropriate birth control

10. Women who are lactating and breast feeding

11. Concurrent medications:

   a. All diuretics except amiloride
   b. Haloperidol
   c. Clozapine

12. Active substance abuse:

   a. Active alcohol or opiate dependence requiring medically supervised withdrawal and stabilization
   b. Active cocaine, methamphetamine, other stimulant, hallucinogen, or cannabis abuse requiring stabilization

13. Enrollment and active participation in another randomized interventional clinical trial

<u>Rationale:</u>

Most diuretics and ACE inhibitors decrease renal excretion of lithium, potentially increasing lithium levels. The only diuretic allowed in the study is amiloride. Subjects on ACE inhibitors/AR blockers and amiloride can be admitted.

The starting dose of lithium will be 300 mg. Subjects on antihypertensive medications will need to be on a stable dose, defined as being on the same does of antihypertensive medication for at least one week while achieving adequate blood pressure control. Monitoring will be intensified with lithium levels obtained monthly throughout the study once they are at steady state. Patients starting diuretic(amiloride) and ACE inhibitors/AR blockers may continue study medication at a reduced dose and increased monitoring as described in "Ongoing Dose Adjustments" in Section XIII).

Patients taking haloperidol are excluded because there are concerns of specific interactions with lithium in the central nervous system. Patients taking clozapine are excluded because its indications, treatment-resistant schizophrenia and reducing recurrent suicidal behavior in schizophrenia or schizoaffective disorders, are not compatible with the inclusion criteria.

VI. STUDY MEASURES

The baseline assessment will collect basic information including race, ethnicity, educational attainment, period of military service, combat exposure, and marital status. Tables 1 and 6 summarize the other data to be collected, their source, and the estimated time required of the participant.

Primary Outcome

The primary outcome will be time to the first repeated episode of suicidal self directed violence including (non-fatal) suicide attempts and deaths from suicide over the one year follow-up period. Interrupted attempts and hospitalizations specifically for the prevention of suicide will be considered equivalent to attempts. To minimize variability and bias in identifying episodes of suicidal self-directed violence, the Outcomes Adjudication Committee will review all potential outcome events, and make final determinations about which should be considered.

The nomenclature and definitions for suicide-related behaviors will follow CDC definitions (Crosby et al., 2011). By definition, an attempt must be accompanied by a wish to die, either reported by the patient, or inferred on the basis of his or her behavior. Repeated suicide attempts are clinically significant outcomes and a proxy for death from suicide.

The study will utilize all available sources of information about repeated suicide attempts including the medical record and VA-Suicide Prevention and Application Network (SPAN) data. As proposed in the draft FDA guidelines for clinical trials in suicide (*FDA Suicidal Ideation and Behavior Draft Guidance*, 2012), the study will utilize the Columbia Suicide Severity Rating Scale (CSSRS; Posner et al., 2011) , supplemented with additional information about preparatory behavior, interrupted attempts, and other forms of self-directed violence (e.g., whether the events was a suicide attempt, an event of undetermined intent, or non-suicidal self-directed violence) to align the CSSRS with the recently adopted CDC classification system (Crosby et al., 2011). The need for additional information to allow cross-walking between the Columbia and CDC approaches has been documented by the Matarazzo et al. (2013).

For reports of suicide attempts, self-report data from the CSSRS will be supplemented with information from the Suicide Intent Scale (Beck et al., 1974) to allow further characterization of attempts, and to distinguish impulsive from non-impulsive attempts (Spokas et al., 2012). For these analyses, attempts will be considered to be impulsive when the patient reports no premeditation on the Suicide Intent Scale.

Adjudication of Primary Outcome

An Outcomes Adjudication Committee will review redacted documents of possible attempts and related events, analogous to the procedures used in the InterSept study of clozapine for preventing suicide-related behaviors in patients with schizophrenia (Meltzer et al., 2003). Reports using a modification of the template of Brown and Holloway (Brown & Holloway, 2005) for use in clinical trials of Cognitive Therapy for Suicide Prevention (Brown et al., 2005) will be submitted to the Outcomes Adjudication Committee for each episode considered to be a possible suicide attempt, an interrupted attempt, another form of self-directed violence, a death from suicide, or an accident.

There will be at least 3 members of the Outcomes Adjudication Committee. Two members will classify endpoints for each case. Cases will be regularly sent to the committee and reviewed independently and blinded to treatment assignment. A third review will be conducted if there is disagreement. The Committee will classify events as suicide attempts, interrupted suicide attempts, hospitalizations where patients were admitted specifically to prevent suicide, and deaths from suicide, all considered as primary outcomes, or as other types of events.

To determine whether an event is an outcome, the Outcomes Adjudication Committee will review all available information. The reports from the study sites will include a narrative of the event from the patient's perspective, information about the method used; the lethality of the method; mood, thoughts, and feelings prior to the event; the nature of planning and preparatory behaviors prior to the event; external triggers; location; whether or not the patient notified anyone prior to and/or after the event; and the nature of the path that led from the event to clinical care. For events that are interrupted by others or by the patient, the report will provide details about what triggered the interruption.

To allow them to determine whether inpatient admissions were done to prevent suicide attempts or to reduce the risk for suicide, the materials to the Outcomes Adjudication Committee will include the patient's explanation of the reason for admission, VA medical records, and discharge summaries from non-VA facilities using authorizations obtained from the patient as part of the consent process.

One of the most important judgments to be made by the Outcomes Adjudication Committee will be whether there was lethal intent. For this purpose, the reports assembled by the Research Teams at the study sites will include information about intent in the patient's own words. The Committee will review all available information, including copies of relevant notes from the medical records, rather than the relying solely on the opinion of the investigator or the patient's clinician. To minimize drift over time, the Outcomes Adjudication Committee will review and rate the training materials on the CSSRS as described in "Training on Study Measures" in Section XVII.

Other Outcomes

In addition to repeated episodes of suicidal self-directed violence, the study will obtain data on a number of secondary outcomes within the 12 month follow up period. These will go beyond the time to the first outcome event to include the total numbers of suicide attempts, interrupted attempts, hospitalizations for the prevention of suicide, emergency department visits, non-suicidal self-directed violent behaviors, and deaths from suicide, unnatural deaths, and all-causes. To support exploratory analyses on subtypes of suicide attempts, the study will obtain data on impulsive and non-impulsive attempts.

Following the total number of suicide attempts and time to the first attempt will allow comparison of our findings with other studies that used rates of attempts as an outcome. Following the impact of the study treatment on other forms of self-directed violence will allow us to explore the specificity of the observed treatment effects. The proposal to evaluate treatment effects on all unnatural deaths and on all-cause mortality follows from concerns that deaths from other causes in patients who have survived suicide attempts may represent suicide-equivalents or cases misclassified by medical examiners or coroners. However, we recognize that the observed rates of all-cause of mortality in persons who have attempted suicide are lower than reattempt rates, and, therefore, the study would not be powered to detect a treatment effect on overall mortality. Finally, exploratory analyses on impulsive versus non-impulsive attempts, defined on the basis of reports of the absence or presence of premeditation on the Suicide Intent Scale, may provide further insights into whether any observed effects of lithium could be related to a decrease in impulsive behaviors.

Covariates

Measures of potential effect modifiers will include traits of impulsivity and aggression. Measures of potential mediators will include symptoms of the patients' affective disorders (including suicidal ideation).

VII. BIOSTATISTICAL CONSIDERATIONS

Overview

The primary hypothesis is that lithium is superior to placebo for the prevention of episodes of suicidal self-directed violence, including suicide attempts, interrupted attempts, hospitalizations to prevent suicide, and deaths from suicide over the ensuing year. The primary outcome measure is time from randomization for treatment allocation to the first episode. The results for event-free survival will be analyzed by means of a two-sided log-rank test. The study will have one interim analysis and one final analysis.

The duration of the study will be 4.5 years total, which allows for 3 years of recruitment, 1 year of follow-up for all enrollees, and time for start-up and closeout as indicated. A total of 1,862 patients will be enrolled and randomized to receive either lithium or placebo, both in addition to

enhanced usual care. We expect to enroll an average of 65 patients per site at 29 VA medical centers. All subjects will be followed for 12 months after randomization. Section IX describes site identification and recruitment plans.

Estimated Incidence of Primary Endpoint

We posit a 1-year event rate of 15% in the placebo group for the primary outcome based on data from the literature on lithium and SPAN data.

Lauterbach et al. (2008) reported a 12% 1-year reattempt rate in the placebo group in a cohort primarily of women, slightly younger than the VA cohort, and predominantly with major depressive disorder. This rate is slightly lower than that projected for the current study possibly because hospitalizations to prevent suicide were not included. Oquendo et al. (2011) evaluated suicide attempts and suicide events separately. Reattempt rates at 1 year were approximately 12% and 18% in the lithium and valproate groups respectively. In spite of their small samples and a more rigid definition of the endpoint, these two trials provided point estimates of outcome event rates between 12% and 18%.

To obtain a more precise estimate of the event rate in the Veteran population, we used VA SPAN data from second half of FY 2010 through the first half of FY 2012 (24 months), to characterize the target Veteran population potentially eligible for the proposed study. Detailed analysis of this cohort is presented in Section IX and selected characteristics of this target population are included and compared to the participant profiles of prior studies in Table 2.

Overall, there were 27,128 veterans with bipolar or major depressive disorder, who survived an attempted suicide between 4/1/2010 - 3/31/2012, a 24 month period. After considering exclusions for 6+ prior attempts, co-morbid conditions of schizophrenia, congestive heart failure, renal failure, lithium therapy within the past year, or use of medications that may interact with lithium, approximately 17,656 subjects (65%) remained potentially eligible for CSP590. According to SPAN data for a subset of the eligible cohort with at least one year of follow-up, 15.2% had repeated episodes of suicidal self-directed violence.

Using event rates from SPAN and the literature, we used a 12 month estimate of a 15% repeat rate in the control population to estimate our sample size and to determine feasibility.

Estimated Effect of the Intervention

In Table 2, we summarize key studies that provide estimates for the efficacy of lithium in reducing suicide rates in depression and bipolar populations. In their prospective cohort study of approximately 20,000 subjects with bipolar disorder, Goodwin et al. observed a 41% to 60% reduction in suicidal events for those on lithium compared to other pharmacological agents. In their meta-analyses of lithium studies, Cipriani and Guzetta demonstrated larger effect sizes ranging from 74% to 88%. Together, these studies support estimates of effect sizes for lithium for reduction of suicide events of 50% or greater and we expect to observe a similar reduction in CSP590.

For the proposed study, however, Lauterbach's placebo-controlled clinical trial in a sample with a large proportion of patients with depressive disorders and Oquendo's valproate-controlled clinical trial in a sample of bipolar patients are also relevant. A reduction of 48% in 1-year reattempt rates in the lithium group relative to placebo was reported in the Lauterbach study, and approximately a 33% reduction in the lithium group relative to valproate group was observed in the Oquendo study.

To be conservative, our sample size estimate is based on an initial estimate of a 43% effect, the weighted average of the 48% reduction effect observed in the Lauterbach study and the 33% reduction effect observed in the Oquendo study. We adjusted for a potential attenuation of the effect due to non-adherence; estimating 15% non-adherence leads to a final estimated effect size of 37%. As discussed below, correction for the loss of data from patients who dropout is addressed through estimates of the sample size requirement, not the effect size for the intervention.

Missing Data from Attrition

In randomized clinical trials, Lauterbach (2008) and Oquendo (2011) reported overall attrition rates of 58% and 50% in the lithium group respectively, of which 21% and 11% were treatment related. Moreover, Lauterbach reported a similar rate of attrition for the placebo group, suggesting that there was no differential dropout.

The proposed study, unlike the previous trials, allows for continued enrollment of subjects who discontinue study medications. The sample size calculations are based on a dropout rate during the course of the study of approximately 40%, or assuming that the dropout rate is uniform, a reduction in the effective sample size of approximately 20%. Allowing for up to 40% dropout or approximately a 20% loss of data for reasons unrelated to treatment, the statistical power calculation is based on an effective sample size of 1,490 evaluable patients from a total of 1,862 enrolled. For the primary time to event analysis, we will censor follow up at the first occurrence of the primary endpoint event, death, or withdrawal from the study for any reason.

We will test the missing at random assumption using a Bayesian Pattern Mixture Missingness approach (Rybin et al., 2013), to validate the results and identify potential bias from possible non-random patterns of missing data. For secondary longitudinal analyses, we will evaluate missingness patterns and perform sensitivity analysis based on multiple imputation methods.

Non-Adherence to Study Protocol

Estimates of the extent of full or partial non-adherence to lithium range from 20-60% (Goodwin & Jamison, 1990; Lingam & Scott, 2002). Findings from a long term follow-up study of patients in a lithium clinic (Maj et al., 1998) and from two large studies using pharmacy data are within this range (Johnson & McFarland, 1996; Kessing et al., 2007). In recent studies, Nierenberg et al. (2013) studied optimized personalized treatment with and without lithium in bipolar subjects and observed that 21% of the participants discontinued lithium prematurely during a six month trial; the BALANCE group (2010) observed that 40% discontinued prematurely in a two year trial.

The most relevant information on tolerability and adherence in a population similar to CSP 590 is from the two studies of lithium for the prevention of suicide. The overall discontinuation rates for the Lauterbach (2008) study (including discontinuations related to suicide and suicide attempts) were 9.5% for the lithium group and 16.7% for placebo at 1 month, 27.3% and 32.5% at 3 months, 32.5% and 35.7% at 6 months, and 57.1% and 59.0% at 1 year. When discontinuations due to suicide and suicide attempts were excluded, the rate for discontinuation during the year was 50%. Because these occurred throughout the year, and because informative data after randomization were obtained on almost all patients, the decrease in the effective sample size was approximately 25%. Dropouts due to the subject's discontinuing treatment were only 10.9% and 12.5%. For planning CSP590, we allowed for potential attenuation of the treatment effect from non-adherence in 20% of the sample. This is reflected in the sample size calculations as an attenuation of the effect size for lithium.

Randomization Plan

The MAVERIC Cooperative Studies Program Coordinating Center (MAVERIC CSPCC) will be the coordinating center for the trial. The Albuquerque VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC) will manage drug inventory and accountability. Patients will be randomized to lithium or placebo by the MAVERIC CSPCC in Boston, in coordination with the CSPCRPCC in Albuquerque.

Both stratification and blocking will be utilized to control for potential imbalances in randomization. The randomization scheme will be stratified by participating site in addition to diagnosis (bipolar vs. depression) and history of prior attempts other than the index attempt (none vs. 1+ attempt). Stratification by site is necessary because of possible regional differences in clinical practices. Participants will be randomized to either lithium or placebo within permuted random blocks of 4 so that the treatment arms are balanced after every 4^{th} randomization within the 4 strata at each site: bipolar with prior attempt, bipolar without prior attempt, depression with prior attempt, and depression without prior attempt. Breaking the blind at the end of each participant's time in the study is not expected to provide information about the treatment assignment of participants remaining in the study as block randomization is within multiple strata. Regardless, an extra treatment assignment will be inserted to each stratum of four to disrupt the blocks and make block size harder to discern.

A web-based randomization program validated by the MAVERIC CSPCC will be provided to study sites. At subject enrollment, Site Coordinators will enter the patient ID number, study site, and eligibility information into the randomization program to confirm that all eligibility criteria are met. If met, the program will select the first unused entry from the pre-specified list of random treatment assignments for the particular site. The lists will be stored on a secure server at MAVERIC CSPCC. In case the electronic system is down, the identical process can be followed manually and the randomization scheme telephoned or faxed to the site.

This CSP clinical trial is a double-blinded study in which neither the patient nor the site investigator knows to which of the two study arms the patient has been assigned. Emergency drug code envelopes will be prepared by the CSPCRPCC and shipped with the study drugs to the Pharmacy Service of the participating medical center prior to the study starting. Each envelope is numbered with a unique patient randomization number and contains the treatment assignment for

that patient. These envelopes are placed in the custody of the Pharmacy Service for the duration of the study. The blind (or treatment assignment) will only be broken if knowledge of the specific drug is essential to the medical management of the patient (See DTHP Section 11 for further information on emergency unblinding of a participant during the study), or at the completion of the study and transfer of care to primary providers (See Section XIV).

The emergency drug code envelope and its contents must be returned to the CSPCRPCC within 72 hours of the code break. Upon receipt of the code envelope, the CSPCRPCC will immediately inform the study biostatistician via telephone or email and send the envelope, which will be filed with the study documents at the MAVERIC CSPCC. When the study has been completed (or terminated early) the unopened envelopes must be returned to the CSPCRPCC. The CSPCRPCC will verify that the envelopes were or were not intact and notify the study biostatistician of their status.

Primary Data Analysis Plan

The primary analysis will be an intention-to-treat survival analysis of all subjects who were randomized and received at least one dose of study medication. The primary hypothesis to be tested is that lithium augmentation of enhanced usual care is superior to enhanced usual care plus placebo for the prevention of repeated episodes of suicidal self-directed violence over time. We posit a one-year repeat rate of 15% in the placebo group and a 37% reduction of events in the intervention group.

The null hypothesis is that the two treatment groups do not differ in their hazard rates. The alternative hypothesis is that the group on lithium augmentation has a lower hazard rate than the placebo augmentation group.

<u>The primary hypothesis can be stated as follows.</u>

> Under the null hypothesis: The 1-year event rate will be 15%.
>
> Under the alternative hypothesis for patients treated with lithium: The 1-year event rate will be 9.45%.

The reductions attributed to treatment may be viewed in several ways. The absolute reduction from 15% to 9.45% is 5.55%, the relative reduction is (15 – 9.45)/15 = 37%, and the hazard ratio (treatment hazard rate/control hazard rate) of 0.61 is approximately midway between the simple odds ratio, [9.45(100-15)] / [15(100-9.45)] = 0.59 and the risk ratio 9.45/15 = 0.63.

The formal hypothesis test is two-sided allowing for lithium augmentation therapy to be either more or less effective than placebo augmentation of enhanced suicide prevention management. However, the study of lithium will only be viewed as successful if patients augmented with lithium have a significantly lower hazard of repeated events than patients not treated with lithium.

We will test this hypothesis with a log rank test, followed by Cox proportional hazards regression modeling to provide the hazard rates, their ratio and the 95% confidence interval

about the ratios. We will also fit a random effects or frailty model to investigate potential heterogeneity of effect due to site variability (Glidden et al., 2004; Hougaard, 1991).

Interim Analysis

We will conduct one interim analysis after half of the participants have completed their 12 month follow up. Assuming a uniform rate of enrollment, it will take 1.5 years to enroll half the sample. Allowing for the last patient to accrue 12 months of follow-up, the interim analysis should take place approximately 2.5 years after initiation of enrollment, at which time, after adjusting for attrition, there should be a sample of 746 evaluable subjects, (373 in each group).

Projecting the same event rate in this sub-sample we expect a 15% repeat rate or 112 events (56 events in each group) under the interim null hypothesis that event rates are equal in the intervention and placebo groups. Under the interim alternative hypothesis, the absolute reduction from 15% to 5.3% is (15-5.3) = 9.7%, the relative reduction is (15-5.3)/15 = 65%, and the hazard ratio (treatment hazard rate/control hazard rate) is 0.34.

Using the O'Brien-Fleming procedure, (Turnbull & Jennison, 2000), this analysis will have a Type I error of 0.2%, which negligibly decreases the overall Type I error for the study and has virtually no effect on the power for primary analysis. The interim analysis is two-sided, and the interim null hypothesis will be rejected if the hazard ratio exceeds 1/0.34= 2.94 or falls below 0.34.

We considered earlier times for interim analyses, but rejected this idea because we would have only modest power to detect very large effects with even smaller sample sizes. Of note, the effects reported by Cipriani and Guzetta (Table 2) are similar or greater than the effects to be tested in the interim analysis. We will confer with the Data Monitoring Committee members and the program leadership for potential stopping guidelines based on efficacy findings from the interim analysis.

Sample Size and Statistical Power Considerations for the Primary Hypotheses

The results for the primary outcome measure will be analyzed by a two-sided log-rank test to detect either a hazards ratio that exceeds 1/0.61=1.64 or is less than 0.61. The test will have a two-sided 5% type I error overall. The test has 90% power to detect a hazard ratio of 1.64 or larger or 0.61 or less with a total of 1,862 patients, 931 per study arm which reduces to 1490 evaluable patients. This allows for 40% of subjects lost to follow-up resulting in a 20% complete data loss while on study before a repeat suicide event is observed.

Tables 3a, b, and c below consider three scenarios for possible shift in statistical power, specifically (1) in the event that an intervention effect different from the projected 37% reduction is observed (Table 3a), (2) in the event that the sample size for the study falls either above or below the targeted 1490 evaluable subject mark (Table 3b), and (3) in the event that the event rate is below the expected 15% in the placebo group. This study will have greater than 80% statistical power at 5% overall error if the observed effect is as low as 33% reduction, if the final evaluable sample is as low as 1200 subjects, or if we observe an event rate as low as 12% in the placebo group.

Secondary Data Analysis Plan

Our secondary analyses are intended:

(a) To explore the effectiveness of lithium augmentation of enhanced suicide prevention management in preventing separately:
1. all-cause mortality
2. impulsive suicide reattempts
3. non-impulsive suicide reattempts
4. self-directed violence

(b) To explore heterogeneity of response to treatment in subgroups including:
1. categories of age, race/ethnicity, and gender
2. diagnosis of depression vs. bipolar disorder
3. impulsive index attempt vs. non-impulsive index attempt
4. substance use vs. absence of substance use
5. individuals with and without trait impulsivity
6. individuals with and without trait aggression
7. subjects who have vs. have not received evidence based psychotherapies

(c) To explore the effect of lithium augmentation of enhanced suicide prevention management on total occurrence of all event types combined and individual event type as follows:
1. all suicide attempts
2. all suicide attempts plus interrupted attempts
3. all hospitalizations for the prevention of suicide
4. all self-directed violence
5. all emergency department visits

(d) To explore longitudinally the effect of lithium augmentation of enhanced suicide prevention management on symptoms of bipolar disorder and depression and suicidal ideation

(e) To explore mediators of the effect of lithium augmentation on prevention of episodes of suicidal self-directed violence, specifically improved control of symptoms and lithium plasma levels

Secondary objective (a) will use a time to event, survival analysis to determine whether there is a treatment difference in event rates for each of the defined endpoints. The null hypothesis for each endpoint is that the two treatment groups do not differ in their hazard rates. The alternative hypothesis is that the intervention group on lithium has a lower hazard rate than the placebo group. The log-rank test and Cox proportional hazards models will be used.

For secondary objective (b), the null hypothesis for each of the factors is that treatment effect does not differ over levels of the factor. The alternative hypothesis is that there is differential treatment effect over levels of the factor. Effect modification will be tested through the use of interaction terms in the Cox proportional hazards regression model with main effects of treatment and factor and an interaction of the two. A forest plot will be used to display the results.

Secondary objective (c) will be evaluated using Poisson regression to model for grand total numbers of events and for total number of each event type controlling for follow up time. The null hypothesis for this objective will be that total event rates do not differ by treatment assignment. The alternative hypothesis is that there is a difference in total event rates across treatment groups.

Secondary objective (d) will be evaluated using mixed effect models allowing for random variation in symptoms of bipolar disorder and depression at baseline. The null hypothesis for this objective will be that change in symptoms and suicidal ideation in the lithium group is similar to that of the placebo group. The alternative hypothesis is that there is a difference in change across treatment groups over time.

Secondary objective (e) will be evaluated by regression analysis method comparing regression coefficients for treatment effect in the models with and without the mediator (Sobel, 1982), as well as by bootstrapping methods, (MacKinnon et al., 2002; Preacher & Hayes, 2008; Tein & MacKinnon, 2003).

Tertiary Data Analysis Plan

These exploratory objectives (explained further in Section XIV) are to analyze electronically available data over the extended follow up period to:

(a) describe pattern of Lithium use following active participation in the study participants,
(b) evaluate suicide reattempt and all cause mortality over a longer follow up period, both for the study population and patients who were evaluated for enrollment under HIPAA waiver ("pre-screen" population), and
(c) evaluate all cause mortality over a longer follow up period.

Tertiary objective (a) will be evaluated by descriptive analysis on duration of lithium use, and by regression modeling to determine factors associated with any lithium use within one month following active study participation.

Tertiary objectives (b) and (c) will be evaluated using time to event survival analysis and Cox regression modeling to determine correlates of suicide reattempts and all cause mortality in the study population.

Data Repository

The Boston CSP Coordinating Center will create a data repository under the Boston IRB oversight for research purposes. Data will be housed at the Boston Cooperative Studies Program Coordinating Center and will be made available to appropriately credentialed researchers conducting studies related to suicide, lithium, or other health questions, in accordance with the Repository Protocol and relevant SOPs.

VIII. POTENTIAL PITFALLS OF THE PROPOSED DESIGN AND ALTERNATIVE DESIGN CONSIDERATIONS

Potential pitfalls of the trial include the threats to internal and external validity inherent in any clinical trial and those of particular concern to this study question.

A. Defining inclusion/exclusion criteria and the "indication": The study includes patients with depression or bipolar disorder who have survived an episode of suicidal self-directed violence, and allows enrollment of patients with psychiatric comorbidities other than psychotic disorders, active substance abuse, and dementia. Basically, the proposal is to test the effectiveness of lithium for prevention of suicide-related behaviors rather than the treatment of any specific condition. The study population for this clinical trial is similar to that of the Lauterbach study (2008) while the Oquendo study (2011), in contrast, studied only patients with bipolar disorder. There may be adequate numbers of patients in VA to support a study limited to depression, but not for one limited to bipolar disorder. Nevertheless, the decision to include all potential subjects with an affective disorder was based on the available evidence and was intended to maximize the potential impact of findings, both for VA and beyond.

B. Potential limitations in the accuracy of estimates for the number of suicide attempts and reattempts:

    1. Attempt rates: The number of suicide attempts and the number of unique individuals who have survived attempts are identified in real time by the SPCs. The SPCs also report on deaths from suicide when they become aware of them. Comparing these reports of deaths with those identified through the CDC's National Death Index (after a lag of 2-3 years) demonstrate that facilities are aware of somewhat less than half of all suicides in their population. It is possible that similar limitations in ascertainment apply to suicide attempts as well as deaths, and that the SPC reports may underestimate the number of attempts and the number of survivors. However, ongoing review of the reported attempts has repeatedly demonstrated that there are few, if any, false positives. Therefore, the estimates used for planning this study must be viewed as lower limits for the true numbers of potentially eligible subjects.

    2. Repeat rates: The proportion of attempt survivors reattempting suicide within one year has remained stable in the VA over the past several years. The reported rates are well within the range of those for other studies of preventive interventions (Section VII). Nevertheless, there are two potentially counterbalancing effects that may affect the reattempt rate for study participants. One is that the increased attention and support due to study participation may decrease the rate of reattempts. The other is that supplementing VA's current methods of surveillance with repeated inquiries using the CSSRS may lead to increased rates. There is no way to estimate the magnitude of these effects, separately or in combination, or even to estimate which is likely to be the larger effect. Uncertainty about these

effects must be viewed as a limitation in the calculations of statistical power for the proposed study.

C. Non-adherence with study medication: The study is designed to minimize the number of subjects who would not be able to tolerate lithium. First, the study's standard operating procedures includes a protocol for reducing the dose of study medication to a minimum of 300 mg/day, and maintaining subjects on the highest tolerable plasma level not to exceed the target of 0.6-0.8 meq/liter. Second, the Site Physician may modify the timing of the daily dose, e.g., recommending lithium with meals to decrease rates of absorption, or shifting larger proportions of the dose to the evening to minimize the impact of fine tremor during the day. In addition, as discussed in Section VII, the sample size calculation allows for a moderate degree of non-adherence. The study tests for an effect of lithium of approximately 43% based on the observed effects in the Lauterbach (2008) and Oquendo (2011) studies. The effect size is lower than most of the observational studies and the meta-analysis of randomized clinical trials conducted for other outcomes. The sample size calculations also assume that up to 20% of subjects would discontinue taking study medications, and that this would attenuate the apparent effect of treatment. To summarize, the proposal to test for an effect size of 37% represents a test for a 43% effect attenuated by non-adherence.

D. Feasibility of blinding lithium treatment: We reviewed the literature on lithium to determine the feasibility of maintaining blinding in a placebo-controlled, randomized clinical trial. Searching of the Medline database using the key words lithium AND clinical trials AND the text word placebo identified 18 relevant reports of primary or secondary analyses of placebo controlled randomized clinical trials (Aggarwal et al., 2010; Amado et al., 2005; Bauer et al., 2000; Bell et al., 2005a, 2005b; Bowden et al., 2003, 2005a, 2005b, 2006; Calabrese et al., 2006; Gyulai et al., 2003; Hirschfeld et al., 2003; Nierenberg et al., 2003; Swann et al., 2001, 2002, 2004; Weisler et al., 2011; Willson et al., 2005). Of these 11 were in subjects with bipolar disorder, 2 in depression, and 1 in amyotrophic lateral sclerosis. There were also four reports of studies that evaluated the psychological and physiological effects of lithium in normal subjects. This search did not identify the Lauterbach paper on suicide prevention. Including it, we identified 19 relevant reports. None of them commented on difficulties in maintaining blinding. None of them reported on the subjects or investigators guesses on treatment assignment and tests of their validity.

As another way to evaluate the literature, we reviewed the rationale for the non-blinded study design in two recent open-label randomized clinical trials of lithium, LITMUS and BALANCE. The primary outcome paper for LITMUS (Nierenberg et al., 2013) did not present a rationale for the open-label design. However, the earlier design paper (Nierenberg et al., 2009) stated, "We chose to not blind the clinicians to treatment because the goals of LITMUS are to evaluate treatments that are used in the community and to study the impact of treatment decisions that are relevant to every day clinical practice. Another factor that supports the open design of the study is that because no one knows the effectiveness of flexibly-dosed lithium added to other mood stabilizers, clinicians should be in equipoise..." The primary report of the BALANCE study (2010) stated, "Investigators and participants were aware of treatment allocation because of the

complexities of masking of lithium therapy and the concern that concealment would restrict participation and generalisability." The earlier design paper (Rendell et al., 2004) stated, "In principle psychiatrists espoused double-blind methodology and it was only when they began to contemplate the possibility of not knowing whether a particular patient was on lithium that blind of treatment emerged as a major disincentive to recruitment." To summarize, the investigators in both studies used non-blinded designs primarily because they were concerned that a double-blind design could be a barrier to recruitment and that it might compromise their goals for recruiting representative patients samples, and drawing inferences about effectiveness. Other reasons were, for BALANCE, the difficulties in the logistics of conducted a blinded, flexible dose study of lithium, and, for LITMUS, the presumed lack of any reason for bias. Most significantly, neither of the study reports stated that their decision to conduct a non-blinded studies was a response to the futility of blinding.

Planning members questioned whether the high frequency of side effects in lithium users would compromise blinding but the consensus of the planning group was that the impact of side effects would be minimized by the proposed schedule for titrating doses. Moreover they concluded that difficulties in maintaining blinding could emerge as an issue for a meaningful subset of subjects in a study of monotherapy with lithium versus placebo in patients who are physically healthy and not taking other medications. However, with the complexity of the patient population with its extensive comorbidity and medications for treatment of coexisting conditions, this would occur only rarely in the proposed study.

E. Dropouts, especially differential dropout between the active and placebo agents are always a concern.

1. Minimizing dropouts: Several methods will be used to minimize dropouts. The study will maintain contact with study participants and reach out to those who do not follow-up. Contacts with treating physicians will be maintained and clinic appointment logs will be scanned to identify when participants will be visiting a VA facility for any reason. In addition, written permission to contact family members, friends, or others who would be likely to know the whereabouts of study participants will be obtained at enrollment. Study staff may arrange home visits to conduct interviews, when necessary, or offer assistance with transportation arrangements, and meal tickets.
2. Participants who cannot tolerate study medication, even at reduced doses, will be encouraged to continue study assessments to allow their inclusion in the intention to treat (ITT) analyses and to allow our continued access to their electronic VA records.
3. Analytic considerations: Estimates for dropout, and the probability of differential dropout are discussed in Section VII. For each secondary outcome, all data collected will be used in the repeated measures analyses. If missing data are determined to be informative, sensitivity analyses will be conducted to examine their influence on the treatment comparisons.

F. Safety concerns: Safety, obviously, is a primary concern. Our Safety Program has X essential elements

1. Lithium level monitoring that meets and/or exceeds what is done in usual care practice and VA practice. Labs are done centrally and reported as soon as they are done to the Safety Officer and pari passu to sites.
2. 24/7 availability of a Safety Officer, a senior psychiatrist, backed by a team with internal medicine, nephrology, cardiology experts – all blinded, are available for consultations on a case by case basis.
3. Safety first is the study's priority. This operationalizes a risk-adverse, conservative approach to study drug dosing. Summarized, when there is any doubt, we assume the subject is on active agent (lithium), treat reported or observed symptoms as potential lithium excess, and lower, or hold, or stop study medication (lithium/placebo) when there is any uncertainty or lack of data (lack of contact with subject, lab results, etc.)

The risk of overdosing from lithium can be estimated from the Lauterbach (2008) and Oquendo (2011) studies which found that approximately 1% of participants overdosed on study medication during the course of one year. To decrease the probability of overdoses, study medications will be dispensed in blister cards because this strategy may reduce the frequency of impulsive (though not planned) overdoses. Another strategy will be to limit the amount of study medications dispensed at any one time.

We propose to dispense two one-week blister cards of study medication at a time and to require the return of used blister cards at the next study visit. Study visits for clinical evaluations and blood tests will be after a minimum of 5 days and a maximum of 30 days at a constant dose of study medication (see section XIV for more detail on dosing intervals). Decisions about dose adjustments would be made, and medications would be dispensed, in general by express mail, to allow starting on the new dose approximately 3-4 days after the study visit.

The ideal would be to require exchanging new blister cards for old ones every 3 or 4 days, but this is not feasible. While planning this study, we evaluated the possibility of accelerating the cycles of blood tests, dose recommendations, and dispensing of new medications to allow weekly visits, and dispensing of only one week's medication at a time. However, to do this, it would have been necessary to obtain blood levels after as little as 3 days, too short a time to ensure that steady state was achieved. Although this may have led to some decrease in the risk of serious overdose, it would have been at the expense of less reliable estimates of plasma levels, and an increased risk for dose-related adverse reactions.

To summarize, the protocol as proposed focuses on minimizing the risks of overdosing by dispensing medications in blister cards and in limited amounts, and by requiring the return of old blister cards. The decision to dispense two-weeks' medication at a time reflects a compromise: limiting the amount dispensed and allowing enough time at each dose to achieve steady state while maintaining the burden of repeated study visits at a realistic level.

G. Procedures for monitoring and adjusting lithium levels: Lithium levels will be determined by a Central Lab to ensure consistency as well as prevent accidental unblinding of the local study staff. By contract, the results will be accessible to the MAVERIC data coordinating center within 36 hours of the blood draw, wherein simulated lithium levels for those participants randomized to receive placebo will be calculated. If lithium level results are not available within 72 hours to the local site, consultation with the Central psychiatrist / CSP590 Safety Officer is required.

The MAVERIC data coordinating center will provide the lithium levels (actual level for participants in active group and simulated level for participants in placebo group) to the Site Physician and the Central Psychiatrist/Safety Officer. The Site Physician, after consultation with the Central Psychiatrist/Safety Officer as needed, will make the final dose adjustments and document the dose, using the provided lithium level and all the clinical information available.

Simulated levels will be calculated as outlined in Section XIII.

The planning group considered an alternative proposal in which all dose adjustments would be done by the Central Psychiatrist/Safety Officer on the basis of lithium levels from the laboratory and clinical information from the study site. In this approach, the Site Physician would execute the recommendation by prescribing the recommended dose unless there was a compelling clinical reason to modify it. The principle advantage of this might be less variability between sites in decision-making about dose adjustments. However, the planning consultants felt this process for titration of the medication would be complicated and cumbersome. Specifically, there was a consensus that it would limit the study's ability to respond to what might be subtle indicators about minor side effects or discomforts with the study medication. Accordingly, there were concerns that it might increase the risk of more significant side effects or dropouts.

Other designs were considered including:

1. A randomized controlled trial (RCT) comparing active treatments: This possibility was rejected because, other than lithium, there is no justification for use of any other medication as adjunctive treatment for patients with depression or bipolar disorder.
2. A clinical trial without a placebo comparison: This possibility was rejected because the planning group viewed it as likely that knowledge of whether or not patients were receiving lithium would affect their providers' decisions about other components of treatment and management.
3. Point of Care (POC) Randomization (Fiore et al., 2011): A POC design with randomization to lithium or another psychoactive agent was rejected on ethical grounds. There is no justification for use of any other medication as adjunctive treatment for patients with depression or bipolar disorder. POC with randomization to lithium or to no lithium was judged fatally flawed in that that knowledge of whether or not patients were receiving lithium would affect their providers' decisions about treatment and management. POC was also judged not to be feasible as maintaining safety would require

titrating lithium and monitoring of plasma levels, all procedures that were beyond the scope of a POC study.

IX. FEASIBILITY OF RECRUITMENT

Eligible Veterans Population

For evaluating the feasibility of successfully completing CSP590, we used the VA-SPAN data to identify veterans with bipolar or depressive disorder, who survived a suicide attempt during the 24 month period from the second half of fiscal year 2010 to the first half of fiscal year 2012. The flow chart in Section XXI (Figure 1) describes the process by which we determined the eligible cohort.

During this 24 month period, 28,934 veterans survived an attempted suicide and of this cohort, 17,656 subjects (65%) were potentially eligible for CSP590. Table 4 gives the 50 VA sites with the largest number of potentially eligible subjects for a one year period.

Assuming we are able to recruit approximately 1 out of 5 eligible subjects, full enrollment would require evaluating a total of 9310 potential subjects. Estimates of the number of study sites required to achieve this target are given in Table 4. Assuming participation of all sites with high numbers of potentially eligible subjects, the minimum number of sites that would be required is 21. A more conservative estimate used the actual sites that agreed to participate and the estimate that 20% of potentially eligible subjects would be recruited. Based on these calculations, we are proposing to include 29 sites.

Also in support of the feasibility of our protocol which calls for titration and blood collection, we have data (not shown) that approximately 70% of those who survive suicide attempts live within 60 miles of a VA medical center.

When identifying the 29 VA sites, we will utilize the CSP **N**etwork **o**f **D**edicated **E**nrollment **S**ites (NODES) whenever possible. As a consortium of VA medical centers dedicated to the multi-site clinical research mission of CSP, it represents sites that should be well-equipped to conduct this study. Eight of the NODES sites (San Diego, Houston, Minneapolis, Dallas, Hines, Palo Alto, Salt Lake City, and Portland) are in the 50 top sites for potentially eligible subjects for this proposed study. Together, they would contribute approximately 2707 potentially eligible subjects over three years, or almost 30% of the total required.

Site Selection

To assist with site selection for CSP590, a survey was conducted on a total of 70 sites comprised of the top 50 sites identified in Table 4, 3 additional CSP NODE sites that were not in the top 50 list, and 17 sites which independently expressed interest. From the 40 sites that returned the survey, the top 29 with the largest pool of potentially eligible subjects have been identified. In addition, 2 VISN1 Clinical Research sites have been added to maintain the enrollment estimate needed for CSP590, but will be included in the Boston site.

Experience with the SAFEVET Program

The experience of VA's Center of Excellence for Suicide Prevention in Canandaigua addresses the feasibility of recruiting suicidal Veterans. The SAFEVET program was implemented from 2009 to 2012 as a demonstration project to evaluate a model for providing follow-up services for Veterans who came to VA emergency departments after a suicide attempt but did not need inpatient care.

During the 3-year project, 1781 Veterans came to participating VA emergency departments after a suicide attempt and were not admitted directly to inpatient units. Of these, 95 (5.3%) refused to participate in SAFEVET; 46 (2.6%) were excluded for other reasons, and 30 (1.7%) were admitted to an inpatient unit within 24 hours of the initial emergency department visit. 388 (21.8%) did not participate for reasons that were not reported to the project's Principal Investigator. Overall, 1222 Veterans (68.6% of the population) enrolled in the project. The outcomes of the program are being evaluated.

Most relevant to the proposed trial, the proportion of potentially eligible Veterans who refused participation in SAFEVET was between 5.3%, the proportion refusing, to 27.1%, the percentage refusing and not enrolled for unknown reasons. The SAFEVET program is substantially different from the proposed trial but shows it is possible to enroll a substantial majority of Veterans who survive suicide attempts to participate in an evaluation of a program aimed at suicide prevention.

X. POTENTIAL BARRIERS and STRATEGIES TO OPTIMIZE RECRUITMENT

Only two randomized trials have been conducted to determine whether lithium can prevent suicide. Both failed because they were unable to recruit adequate numbers of patients. In both studies, subjects were recruited from a small number of hospitals and clinics, and surveillance for potential subjects was established de novo for the study. Moreover, many potential subjects had no ongoing connection with the hospitals or mental health providers associated with the study.

In contrast, our study would be conducted within a large comprehensive health care system with an electronic medical record, an established patient population, a highly organized and standardized system for the management of suicide risk and a unique system for active case-finding of patients who have attempted suicide. All of these factors should increase the likelihood of accomplishing our recruitment targets and should overcome most of the barriers that limited recruitment in the prior studies. Put in another way, since 2007, the VA has developed the infrastructure for studies such as the one proposed here as it established VA's program for suicide prevention.

Additionally, study visits and blood draws may take place at Community-Based Outpatient Clinics (CBOCs) under the same Federal Wide Assurance as the approved participating medical center to allow more flexibility and convenience for the participants. Thus, selected sites that are able to meet the requirements of the protocol will utilize VA telehealth (VTel) at CBOCs for study visits - both titration and steady state - and laboratory monitoring.

The director of the CBOC will provide a letter of support to conduct study visits at the CBOC. CBOC staff will provide standard-of-care/practice services they would normally provide and have have the capacity to carry out the procedures required by the protocol (e.g. vital signs, phlebotomy, EKGs, etc). It is expected that study sites may have different work flows to meet the requirements of the protocol.

The number of unique survivors of attempts by facility is information only available within VA. Unlike previous research, planning of this study went beyond the use of basic epidemiological findings to estimate the availability of potential subjects; it utilized counts of specific subjects in specific facilities rather than estimates from the literature or similar populations.

In addition, the study will use the SPAN database to identify potentially eligible patients at each site. Participating sites will send the Boston Coordinating Center their screening logs on a monthly basis. The Coordinating Center will compare those patients already screened by the sites against new persons recorded in the SPAN database to increase the pool of potential participants.

Our survey of VA psychiatrists (Section III) also demonstrates strong support for the study from clinicians in the field. Findings from SAFEVET (Section IX) suggest that those patients who have attempted suicide will at least consider participation. These findings can inform estimates of the magnitude of provider-related barriers, and at least the initial component of patient-related barriers. They suggest that the estimate that 20% of eligible patients can be recruited should provide a margin of safety adequate to ensure that this study can meet targets for enrollment.

The study is built upon recognition that an attempted suicide and related behaviors are highly emotionally charged events in the lives of veterans and their families, and that the processes for obtaining consent, establishing eligibility, randomizing treatment, and maintaining subjects under double blind conditions for a full year are major challenges. Preliminary discussions with survivors within the VA have suggested that participation in research can, to some extent, represent an opportunity for individuals to transcend their suffering and to use their experience to help others. Nevertheless, the investigators recognize that staffing for the study and its implementation must reflect sensitivity, cultural competence, and caring for Veterans in a high degree of distress and for those who would prefer to deny the significance of their attempt. These issues will be addressed during site selection and staff training. In addition, we will have regular telephone conferences for Site Coordinators to review the issues that have arisen during recruitment, to share lessons learned, and to engage the broader group in problem-solving.

XI. PATIENT ENROLLMENT

Maintaining Awareness

In this, as other clinical trials, it is important to ensure that mental health and medical providers maintain awareness of the study so they can consider referring patients who are potentially eligible for participation. Members of the Research Team will be encouraged to conduct rounds or academic detailing on a regular basis in mental health and primary clinics, pain clinics, emergency departments, inpatient units and other relevant settings. Research Teams will also review admissions to emergency departments and inpatient mental health units on a regular basis

to identify patients who may be eligible, determine whether they have been referred for study participation, and engage in problem-solving to identify and overcome any barriers.

Recruitment, Screening, and Evaluation Procedures

Recruitment: Case identification and recruitment will proceed through the following steps, generally in two or three visits:

1. Veterans who have survived suicide attempts may come to the attention of the Suicide Prevention Coordinators from providers, SPAN, or the Veterans Crisis Line. SPCs will refer the patient to the Research Team at the site.

2. Site Coordinators may also become aware of potential participants through outreach such as scanning admissions and ER logs for events, and IRB approved posters and pamphlets advertising the study.

3. During pre-screening, the research team will review the medical record for information about the recent episodes, diagnoses, and medications.

4. Before contacting a patient directly, the site coordinator must ensure that a member of the patient's mental health care team has introduced the study to the patient and the patient agrees to be contacted by the study team. The method used by the provider to document the permission of the participant to be contacted can be done in the following ways: 1) the provider can document via an encrypted email or 2) a non-VA Mental Health provider can send to a secure faxline or by US mail to study site with permission granted by patient to have the study team contact the potential pariticpant.

   Should a potential participant contact the research team directly to learn more about the research study, a research team member can speak with the potential participant about the study.

5. When a patient appears eligible, consent will be sought. Contact with the patient's mental health provider and provider responsible for the patient's general medical care will be made.

   After ICF 1 (see section XII Human Subjects Issues and Informed Consent) and prior to randomization, documentation of VA MH provider concurrence will be obtained by
   1) an encrypted email, or
   2) secure fax, or
   3) signed CPRS note.

   A non-VA Mental Health provider can send to
   1) a secure faxline or
   2) by US mail, to study site, concurrence of study participation.

6. After obtaining ICF 1 and prior to randomization, documentation of the participant's general medical care provider's (primary care provider's) awareness will be required. This awareness can documented by
    1) CPRS co-signed note, or
    2) read receipt of encrypted email, or
    3) documentation of awareness (e.g. phone or in-person) conversation.

Screening and Evaluations:

First consent [ICF 1]: This consent is limited to screening procedures, describing the purpose and what is involved in the study, and answering any questions the participant may have. It will be made absolutely clear that the screening is not treatment and that going through screening does not obligate the person to participate in the actual study.

During screening, the Research Team will conduct a complete review of the medical record, and, if the patient meets preliminary inclusion/exclusion criteria, the patient's health care providers will be contacted to inform them that the patient is being considered for the study.

The Research Team will conduct evaluations to:

- Confirm that the patient has attempted suicide, experienced an interrupted attempt, or was hospitalized specifically to prevent suicide within the previous six months
- Obtain a history of previous psychiatric diagnoses and previous attempts from the patient and from available medical records
- Conduct structured diagnostic interviews with MINI and the SUD module of the SCID
- Evaluate cognitive status with the OMC
- Evaluate decision-making capacity/competency for consent using Jeste's brief instrument for assessing decisional capacity (UBACC)
- Identify and obtain contact information for family member(s), friend(s), or other contact that could provide information about the participant's whereabouts if the participant cannot be reached by the research team.
- Document all medications (prescribed and over-the-counter) including those prescribed within and outside of the VA .
- If the Veteran agrees, the Research Team will include family members and significant others in discussions about the study and the Veteran's participation.

Second Consent [ICF 2]: Before randomization, the Research Team will seek the final consent for the individual's participation in the randomized trial, after discussing the consent form with the patient (and others as appropriate), to be sure that the participant is fully aware of the procedures, the meaning of randomization, the potential benefits and risks of participation, and that they want to participate.

To avoid unnecessary costs and inconvenience screening laboratory tests and screening EKG will only be done if the person consents to the actual trial. Final screening procedures that are done after ICF 2 is obtained include labs (CBC, TSH, creatinine, electrolytes, and calcium levels), EKG and Physical Exam. (If the EKG and / or Physical Exam have been done within the past 30 days, they will not have to be repeated.) Research staff who routinely perform medical or physical exams under their scope of practice are allowed to perform these exams for this research study.

A urine pregnancy test will be performed at each study visit for those participants of childbearing potential.

XII. HUMAN SUBJECTS ISSUES AND INFORMED CONSENT

Process for obtaining informed consent

There are two Informed Consent documents for this study:

1. ICF 1: [Part One: Screening for Eligibility] seeks consent to screen the patient for eligibility for the clinical trial, and

2. ICF 2: [Part Two: Randomized Trial] seeks consent to further evaluate the patient for eligibility with a physical exam, EKG, and laboratory tests, and ask potential subjects who meet inclusion and exclusion criteria after preliminary screening whether they consent to study participation if they continue to be eligible.

The initial phase (under ICF 1) of the consent process will focus on the details of the evaluations and a general outline of the treatment study. The second phase (under ICF 2) will focus on the details of the actual clinical trial.

Overall, the consent process will explain the purpose of the study and describe the treatments. The randomization process, the necessity of blinding, the timeline, and what is expected of the patient will be reviewed. The risks associated with lithium and study procedures (e.g., venipuncture) will be addressed. The procedures and safeguards for maintaining strict confidentiality will be described.

If the patient consents to participate in the study, each phase of informed consent (ICF 1 and ICF 2) will be documented per VA guidelines. The original documents will be placed in the Local Site Investigator's Master Consent Binder. Copies of signed Informed Consent documents will be provided to the participant, placed in the participant's study file, and securely transmitted to the MAVERIC CSPCC.

Informed consent requires that the participant understand the details of the study and agree, without coercion, to participate in the study. To obtain informed consent, the following information shall be provided to each participant:

1. Name of the study
2. Name of Site Investigator(s)
3. Explanation that the study involves research
4. Explanation of the purpose of the study

5. Explanation of the study procedures
6. Description of randomization
7. Description of the risks and benefits of participation in the study
8. Description of alternatives to participation in the study
9. Explanation that all records will be kept confidential, but that records may be examined by representatives of the VA and/or the FDA
10. Whom to contact for questions about the research and about subjects' rights
11. Whom to contact in the event of a research-related injury
12. 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
13. A statement that the treatments provided as part of this study are free

Merely obtaining signed consent from the patient does not constitute informed consent. However, the use of a standardized consent form aids in assuring that participants receive adequate and consistent information about the trial and that they have consented to participate.

In conjunction with the informed consent procedure, participants will review and be asked to sign the Authorization for Release of Protected Health Information From as required by HIPAA. As with the informed consent forms, The original HIPAA documents will be placed in the Local Site Investigator's Master Consent Binder and copies of the signed HIPAA forms will be provided to the participant, placed in the participant's study file, and securely transmitted to the MAVERIC CSPCC.

Benefits

General: The information from this study will be of scientific and public health value, helping to guide treatment of individuals at risk for suicide.

For participating subjects: Participants may benefit from the increased monitoring that is related to study participation and through early identification of exacerbations of their mental health condition and periods of increased risk for suicide.

Reimbursement

Participants will receive reimbursement to defray their travel/time based on the distance from their residence to the study site.

Risks

The risks of study participation are related primarily to the risks of lithium administration, including the side effects or adverse reactions that can occur during treatment or when someone stops taking lithium, drug-drug, and drug-disease interactions, and intentionally taking too much of the medication. They also include the risks associated with drawing blood for various tests.

All medications have potential risks. Lithium may cause all, some, or none of the side effects listed below. Rare or unknown risks may also occur. Each study participant will be informed of

any information that becomes known during the course of the study regarding risks of the interventions that might affect their willingness to continue to participate.

Side Effects and Adverse Reactions:

The incidence and severity of adverse reactions from lithium are related to its serum concentrations and to individual patient sensitivity, generally occurring more frequently and with greater severity at higher lithium concentrations. According to the American Hospital Formulary Service (AHFS) Drug Information Service (2012), about 75% of people experience some side effects when they begin lithium. The most frequent side effects include nausea, loose stools, thirst, increase in urination, shakiness of the hand, headaches, sweating, fatigue, decreased concentration, rash, and dry skin. For most people, these are mild and limited to beginning of lithium treatment. The prevalence of some side effects is described below:

> Nervous system: Lithium can cause a hand tremor in almost 50% of people who start taking the medicine, but it persists for one year in less than 10%. Feelings of weakness or a loss of strength can occur in about 30% of people who start lithium, but it persists in about 1%.
>
> Gastrointestinal effects: Symptoms like nausea or vomiting, decreased appetite, loose stools or diarrhea and abdominal discomfort occur in 10-30% of people who start lithium; they persist for up to 1-2 years in 1-10%.
>
> Kidney effects: Increased urination with increased thirst and fluid intake occurs in 30-50% of people who start lithium. By 1-2 years, these symptoms decrease to between 10-30%.
>
> Metabolic effects: Lithium can lead to increases in Thyroid Stimulating Hormone in about 30% of people, clinically significant decreases in thyroid function in 1-4% and goiter in about 5%.
>
> Heart effects: Lithium can cause changes in the electrocardiogram in about 20-30%, but these are usually of no clinical significance. Rarely, lithium can cause arrhythmias or changes in cardiac conduction, usually in people with preexisting cardiac disease.
>
> Skin effects: Dry skin is the most common skin-related side effect of lithium. Rashes occur in about 1%.

A recent meta-analysis of adverse effects observed during long term administration of lithium (McKnight et al., 2012) should be noted even though the study drug is intended for only one year. The synthesis found decreases in glomerular filtration rate and in renal concentrating ability, increases in TSH and clinical hypothyroidism, increases in calcium, in PTH, and weight. It found no increased hair loss or skin disease. Contrary to FDA and other warning sources, it found no increase in congenital malformations but the number of cases was too few to be definitive.

Discontinuation and Withdrawal

That lithium might prevent suicide and suicide-related behaviors is suggested by comparisons of patients currently receiving lithium and those who have discontinued lithium (Muller-Oerlinghausen et al., 1992; Nilsson, 1990, 1999; Schou, 1998; Tondo et al., 2000, 2001), comparisons of behaviors before, during and after lithium treatment (Tondo et al., 1997, 1998), and comparisons of patients taking lithium and other medications. Suicide related behaviors may be more frequent during the first year after discontinuation of lithium than afterwards (Tondo et al., 1997, 1998). The available data do not allow a distinction between an unmasking of suicide-related behavior when lithium is discontinued versus a withdrawal phenomenon. However, there have been suggestions that the increase in the onset of mania, depression, and suicide-related behaviors is lower when lithium is discontinued gradually, over a period of two weeks or longer (Baldessarini et al., 1999a; 1999b).

These issues will be addressed by including information about discontinuation in the consent form, gradual tapering of lithium whenever subjects discontinue treatment, and individualized clinical management at the end of the study.

Drug-Drug Interactions

Potential drug-drug interactions are listed on Table 5 (”Lithobid”, n.d.). These can result either from effects on the renal excretion of lithium and modifications in lithium levels, or from effects on end-organ sensitivity to other drugs. With most medications with potential drug-drug interactions, a patient may be on a drug with potential interaction with lithium as long as there is close monitoring and regular lithium levels obtained.

Drug-Disease Interactions

Lithium may affect the cardiac conduction system and these effects can be of increased significance in those with pre-existing cardiac disease. Lithium may also affect thyroid function in those with thyroid disease; and affect renal physiology in those with mild to moderate kidney disease. These are compatible with study participation with close monitoring for adverse effects as proposed. Patients with renal failure and heart failure are excluded because these conditions are associated with a high degree of variability in lithium clearance.

Toxicity

The concentrations of lithium that may be toxic (1.5 mEq/L or greater) are close to the concentrations that are generally considered to be within the therapeutic range (0.6 to1.2 mEq/L). Diarrhea, vomiting, drowsiness, weakness, and lack of coordination may be signs of lithium intoxication. They are most common at lithium concentrations of 2.0 mEq/L or above, but they can occur at low levels. At higher concentrations, giddiness, ataxia, blurred vision, and tinnitus can occur. Serum lithium concentrations above 3.0 mEq/L often lead to severe, dangerous adverse reactions affecting multiple organ systems.

No antidote for lithium is known and treatment for lithium toxicity is supportive. Mild symptoms of lithium toxicity are treated by holding the dose or reducing the drug for 1 to 3 days. In

poisoning, the treatment is: 1) elimination of lithium by gastric lavage, 2) correction of fluid and electrolyte imbalance, and 3) stabilizing renal function. Urea, mannitol, and aminophylline increase lithium clearance. Hemodialysis can be used to remove lithium rapidly in severely toxic patients.

Two studies of lithium in suicide prevention were used in estimating the risks of overdose in this study. In the Lauterbach study (2008), 17 suicide-related events (3 suicides and 14 non-fatal attempts including 13 overdoses) occurred. Two of the overdoses were with study medication, neither fatal, and represented 1.2% of those randomized. In the Oquendo study (2011), there were 18 non-fatal suicide attempts over the 2.5 years of the study. Three of these were with study medication; and represented 2.0% of those randomized.

XIII. TREATMENT REGIMENS

Study medications

Lithium will be provided as extended-release lithium carbonate (or placebo) in 300 mg tablets. Subjects will be started on 600 mg/day (300 mg bid), unless there are clinical indications for starting at a lower dose (300 mg/day). Lithium (or placebo) plasma levels will be determined (by send-out central lab testing) after each dose adjustment (see section XIV, Titration Visits, for more detail) until steady state at target plasma levels between 0.6 and 0.8 mEq/L is achieved. Steady state is defined as a serum lithium level between 0.6 and 0.8 mEq/L, over 2 consecutive visits, at the same dose, and with the second level the same or 0.1 mEq/L lower than the first level. The target range will be operationalized by providing guidance to Site Physicians that they should stop titrating the dose upwards if proportional increases in plasma levels would exceed 0.8 mEq/L, that is, if the steady state plasma level on a dose of 300 mg/day exceeds 0.40 mEq/L or the level of a dose of 600mg/day exceeds 0.53 mEq/L. After steady state levels within the target range are achieved, the frequency of plasma level determinations will be decreased to monthly until the end of six month's participation, and then quarterly unless they are on an ACE inhibitor or a diuretic, in which case monthly monitoring will continue; they will be done more frequently when medically indicated in either the lithium or the placebo group.

The target plasma levels are within the range considered effective for other lithium indications. The 2010 VA-DoD Clinical Practice Guideline for Bipolar Disorder recommends target levels of 0.6-1.0 mEq/L for maintenance treatment; the 2009 VA-DoD Clinical Practice Guideline for Major Depressive Disorder recommends 0.5-1.0 mEq/L for the augmentation of antidepressant responses; and the 2002 American Psychiatric Association Guideline on Bipolar Disorder recommends 0.5-1.2 mEq/L. A 1998 observational study by Tondo et al. found an 85-90% reduction in suicide risk for patients on lithium with average plasma levels of 0.624 ± 0.134 mEq/L. Based on these data, target plasma levels for the Lauterbach study (2008) were 0.6-0.8 mEq/L, similar to those proposed for this study.

On the basis of studies that examined associations between suicide rates and lithium concentrations in drinking water, it has been suggested that lithium may have a preventive effect even at very low plasma levels (Helbich et al., 2012; Kabacs et al., 2011; Kapusta et al., 2011; Ohgami et al., 2009; Schrauzer & Shrestha, 1990). Based on these reports and absence of data

for what constitutes a lower limit for effective plasma levels, dose (and plasma-level) reductions will be allowed for patients who are unable to tolerate 0.6-0.8 mEq/L. The lowest allowable dose of lithium for continued treatment will be 300 mg/day. All patients able to tolerate that dose will be maintained at the highest tolerable plasma level not to exceed 0.6-0.8 mEq/L.

Blinding

This is a double blind placebo-controlled study in which the participant, treating clinicians, and all study personnel, including the Central Psychiatrist/Safety Officer, are blinded to treatment assignment.

All investigators and Outcomes Adjudication Committee members will only see blinded interim reports. Members of the DMC will receive unblinded reports in that they will view study results by treatment group (e.g. A versus B) and these designations will be randomly assigned within a report. The placebo will be produced by the CSPCRPCC and be nearly identical in appearance to the active agent and have similar taste and odor.

Breaking the blind, to the patient's mental health provider, at the end of a participant's time in the study should not compromise the blind for the personnel at the study site nor influence outcome assessments of participants remaining in the study. All ratings and assessments will be completed before the blind is broken. To ensure that the breaking the blind on those who complete the study does not reveal information about the assignment of the last subjects, block randomization is within multiple strata and an extra treatment assignment will be inserted to each stratum of four to disrupt the blocks and mask block sizes, as described in Section VII.

Titrating study medication

The process for titrating study medication at the initiation of study treatment and for maintaining them during the course of the study will be based on real or simulated plasma levels. To ensure local site blinding and standardization of measurements, some blood samples will be sent to a Central Laboratory for analysis. Lithium levels, TSH, T4, and creatinine will be analyzed by the Central Laboratory, while other samples, for complete blood count (CBC) and electrolytes will be sent to the local VA laboratories for analysis.

Lithium levels, creatinine, eGFR, and summary of side effects will be sent to the MAVERIC data coordinating center which will send real or simulated plasma levels and dosage adjustment recommendation to the Site Physician and to the Central Psychiatrist/Safety Officer. A lithium level of 1.2 or above will be considered a potentially dangerous situation and will be automatically sent to the Site Physician as well as the Coordinating Center and Central Psychiatrist/Safety Officer.

The Site Physician will use these levels and a check list review of symptoms at the time of the blood draw to make dose adjustments. During the initial dose adjustments, the Site Physician will typically decide between increasing doses by one pill per day, or maintaining the current dose.

Participants will have titration visits until they reach the target steady state: a serum lithium level between 0.6 and 0.8 mEq/L, over 2 consecutive visits, at the same dose, and with the second level the same or 0.1 mEq/L lower than the first level. It is expected that most patients will titrate within 4-6 visits, but the process may take fewer visits, or may take up to 8. If steady state is not achieved after 8 visits, the Central Psychiatrist/Safety Officer will work with the site on a case-by-case basis to determine a prescribing plan. If participants are not able to tolerate the dose needed to achieve the target level, they will be prescribed their maximum tolerated dose.

If it has been fewer than 60 days from randomization to achieving steady state, the participant's next visit will be a steady state follow-up visit 2 months after randomization (within the window allowed for steady state visits). If it takes more than 60 days, the next visit will be the 3 month steady state visit, and the month 2 visit will be ommitted.

For added safety, the site physician has the capacity to hold study medication for up to three days or decrease the dose as the clinical circumstances warrant. When determining the initial dose of study medication; if the site physician has concerns that factors such as aging, potential drug-drug interactions, or potential drug-disease interactions would decrease the tolerability of an initial dose of 600 mg of study medication, he or she could can reduce the starting dose to 300 mg/day for the first interval.

During the course of the study, there may be unanticipated changes in the patient's medical condition, side effects or adverse reactions to study medication, new prescriptions of medications with potential drug-drug interactions, or other events associated with volume depletion or dehydration that could lead to adverse events through increased the serum level or increased tissue sensitivity. If any of these occur, the site physician may decrease the dose of study medication.

Whenever the site physician holds study medication or prescribes a reduced dose for reasons of safety, he or she will document the reason, and the duration of the "hold" or the actual dose prescribed. Also, at these times, the site physician will monitor the patient closely, e.g., through increased contact by telephone. Depending on the patient's clinical condition, further dose decreases may be necessary; decreases down to 300 mg/day are allowed by the protocol. If the patient is stable, the reduced dose will be maintained for approximately 5-7 days at which time another lithium level will be obtained and used to guide further dose adjustments, as appropriate.

When each patient is entered, the Research Team will forward information on physiological parameters including age, sex, height, weight, medications, medical conditions, and creatinine to the MAVERIC data coordinating center to allow estimations of the lithium clearance using empirical algorithms (e.g., Abou-Auda et al., 2008). At the time that blood levels are determined, the Research Team at the study site will provide the MAVERIC data coordinating center with updated information on laboratory parameters, information about changes in the patient's medications and medical status, and reports from the patient on adherence for study medications and side effects. To calculate the simulated lithium level, the MAVERIC data coordinating center will:

1) Calculate a plasma level for the current dose using the method of Abou-Auda (2008).

2) Adjust the plasma upwards if there are reports of side effects, and downward, if there are reports of non-adherence; these adjustments are intended to ensure that the simulated plasma levels appear plausible and realistic in light of the patient's clinical status.
3) Multiply the adjusted value by a random factor. This is necessary to ensure that there is a realistic degree of week to week variability for simulated plasma levels and that the reported values cannot signal the Research Team at the study site about whether the plasma levels are real or simulated.

During the course of the study, the study biostatistician will periodically compare the distributions of real and simulated plasmas levels to ensure that there are no significant differences. Should there be trends suggesting they are diverging, the biostatistician will work with the MAVERIC data coordinating center to revise the parameters for calculating simulated measures.

All participants will have flags in their VA electronic medical records in accordance with local policy. This study falls under the 1200.05 2012 version, however, we recommend that the flags state that the participants are enrolled in a research study and any medication changes or drug level testing be done only after consulting the Site Physician. The amount of information provided within the flags may vary by site according to local policies and procedures.

The processes for dispensing medication from a VA pharmacy or by mail will be developed for each patient, depending upon whether patients are inpatients (at the start of the study) or outpatients, and whether or not they have convenient access to a VA facility. Medications will be dispensed in blister cards containing medication for two weeks. Some participants may be dispensed one week of medication at a time if the investigator determines this is more appropriate for the safety of the participant. Participants will be asked to return unused blister cards at the next study visit to perform tablet counts to assess adherence.

In general, blood samples, updated medical and psychiatric history, and review of side effects will be obtained on approximately the 7^{th} day (± 2 days) of the dosing interval (see section XIV, Titration Visits, for more detail). Findings will be reported to the Central Psychiatrist/Safety Officer and lithium levels (actual or simulated) under ideal circumstances will be communicated to the site within 48-72 hours.

Once the Site Physician decides on dose adjustments and orders the study medication, the blister card containing the prescribed amount of tablets will be dispensed in person or by express mail.

If, for any reason, the scheduled blood tests are missed, the process for dose adjustment will need to be modified. However, the scheduled assessments will still be completed to guide patient management as well as to ensure ongoing study assessments. The Site Physician may either hold the current dose if there are problems or continue the current dose but may not, to be cautious, increase the dose. If necessary, the subject will be mailed enough blister-packed tablets to cover the time until the next scheduled dose adjustment.

Ongoing dose adjustments

During the course of double-blind treatment a number of events may indicate the need for additional clinical assessments, blood level determinations, other laboratory tests, and, possibly, dose adjustments. These may, for example, include reports of side effects, observations of possible adverse reactions, laboratory measures, changes in medical status, or modifications in medications. When these occur, the Site Physician will conduct clinical evaluations, obtain blood for lithium level and other determinations as needed using the same procedures for planned dose adjustments. Decisions about clinical management of dosing will be the responsibility of the Site Physician. He or she may ask the patient not to take study medications for up to three days, modify the dose on a temporary basis, or modify the dose from that time onward. In general, he or she will continue to monitor the patient with repeated contacts, assessments, blood levels, and other tests as appropriate until the patient's medical status and blood levels stabilize.

Enhanced usual care for preventing suicide

Enhanced usual care is detailed in Section I, Introduction and Background. Each patient's management will meet VA policies and practice guidelines. Patients will be evaluated regularly for titration visits until they reach the target steady state range, then monthly(see section XIV, Titration Visits, for more detail). Management will include safety planning, directions for seeking help on a 24/7 basis, and identification of family members and/or friends who could inform the Research Team about side effects, recurrences, or treatment emergent events. Completion of study visits will meet requirements of enhanced usual care.

Concurrent care for psychiatric and medical conditions

To ensure patient safety, the protocol includes provision for more detailed clinical evaluations and additional blood tests to determine lithium levels (or simulated lithium levels) when there are significant side effects or treatment emergent events. There is also provision for additional evaluations and needed modifications of concomitant treatments whenever there are recurrences or exacerbations of mental health conditions.

Participants receive four types of care: (a) study treatment, (b) management of the risk of suicide, (c) treatment of the depression or bipolar disorder and coexisting mental health conditions, and (d) routine primary care/treatment of coexisting medical conditions.

Treatment with study medications will be the responsibility of the Research Team. Treatment of the depression or bipolar disorder and comorbid mental health conditions will be the responsibility of the patient's mental health providers. Routine primary care and treatment of coexisting medical conditions will be the responsibility of the patient's medical providers. Study procedures, including the requirement for concurrence with participation from the patient's mental health provider, are designed to ensure coordination of the study with clinical care.

The research team will share responsibilities with the participant's mental health provider(s) including the Suicide Prevention Coordinator (SPC) for managing the risk of suicide. Research team members will also share timely information about side effects of medications, changes in mental and medical health and current medications with the participant's mental health and

medical providers as appropriate. The Research Team will follow-up on questions about suicide related symptoms and behaviors by reminding the particpant about the suicide prevention safety plan. When necessary, research staff will contact the SPC and the mental health provider(s) about the need for revising the plan. All research visits will be considered research encounters and no participant or his/her insurance will be billed or charged a copay for these encounters.

The research team will inform a participant's mental health and medical care providers about significant changes in a participant's status. To ensure patient safety, the patient's providers will be asked to communicate changes in the patient's medical status, and any and all new medications prescribed before these medicines are started, to the Research Team. Should the treating mental health provider decide that lithium or haloperidol treatment is essential, the participant will be withdrawn from the trial but be included in the intention-to-treat analysis. In other situations, they will discuss strategies for optimizing the patient's safety in light of possible drug-drug and drug-disease interactions. For example, if patients have new onset hypertension, the physicians will discuss use of medications that minimize drug-drug interactions with lithium (e.g., certain beta blockers or amiloride rather than other diuretics). Other drug choices may call for increased monitoring for plasma levels and side effects and a lowering of lithium doses because lithium clearance may decrease.

When there are new signs, symptoms, or diagnoses of cardiac, thyroid, or renal disease, the provider responsible for the patient's general medical care and Site Physician will jointly evaluate the possible contribution of lithium. Decisions about discontinuing the study medication versus continuation with increased monitoring and modifications in the dose of study medication, as appropriate, will be made on a case by case basis by the Site Physician, and the provider responsible for the patient's general medical care in consultation with the Study Chair as appropriate.

XIV. FOLLOW-UP AND TERMINATION

Titration Visits

All participants will be followed from randomization until the completion of the study (one year of lithium/placebo treatment). Participants will be followed as described in the Schedule of Visits (Table 6). Study assessments will be done at screening, baseline, every 10-14 days during the titration phase (in general, for up to six visits), and monthly until the end of study.

During the titration phase, participants will take the same dose of study medication for a minimum of 5 days prior to having their levels reassessed. Results from the blood draw are available to sites within approximately 3 days of the blood shipment, at which point a new dose may be selected and shipped to the participant if they are unavailable to pick up the prescription. Based on the dispensing of 2 weeks of study medication at a time and that it is necessary to allow a minimum of 4 days after a study visit for processing blood samples, communicating findings to the Central Psychiatrist/Safety Officer, communicating actual or simulated plasma levels to the study site, prescribing, and dispensing medications, there is a window of 10 to 14 days between titration visits. The Site Coordinator can conduct all assessments unless a physical exam is

required. Additionally, it is possible for participants to have unscheduled check-in visits at any time.

During titration phase, each new dose of study medication must be taken for a minimum of five days before collecting and sending another Lithium blood sample.

Steady State Visits

Once participants have reached steady state, study visits will occur every month, with a window from one week before the target date to one week afterwards. For the completion of the study, the window will be between one week before the target date to one month afterwards.

Ongoing Considerations and Special Circumstances

Additional visits will be completed as necessary for emergent events.

Pregnancy testing: At every visit post-randomization, participants of childbearing potential will be reminded of the potential dangers of lithium during pregnany, review acceptable birth control methods, document what method of contraception is being used, and update all medications as well as over-the-counter medications, supplements being used.. If there is reason to doubt the participant's judgment, a pregnancy test will be done. Women of childbearing potential will have pregnancy testing at each study visit.

Participant Pregnancy:
Upon learning of a possible participant pregnancy, the study medication should be held STAT, and the Safety Officer, CSP Coordinating Center (Boston, MA) and local site investigator notified.The pregnancy will be confirmed and the participant will be informed.

Upon confirmed pregnancy, the LSI, participant, and MH provider will be unblinded. As the medical necessity for knowing the identity of the study drug is ultimately the responsibility of the participant's obstetrical and medical providers. The CSP Coordinating Center, Safety Officer, Study Chair and VA Central IRB will remain blinded. The LSI or designee shall, in turn communicate the pregnancy status with both mental health and primary care providers.

If the subject is on lithium, the LSI will ensure that her mental health provider(s), primary care physician, and obstetrician will be made aware of her situation. LSI and study team will recommend that she have ultrasound at 16 weeks of the pregnancy to screen for Ebstein's anomaly. The understanding is that the decision to have an ultrasound is ultimately a decision of the participant in consultation with her pre-natal care providers.

The outcome of the pregnancy and the health of the newborn especially with regard to the presence or absence of Ebstein's anomaly is an area of concern for lithium usage. The CSP Coordinating Center and LSI will follow the individual until the end of pregnancy and the status of the newborn is established. As the delivery will likely occur in a non-VA facility, the review will require all other (e.g. obstetric, neonatal and/or pediatric) medical records be gathered after signed permission.The participant will also be invited for an end of study visit to close out her study record.

Special Circumstances - Involuntary Psychiatric Hold:

In the event that a study participant is placed in an involuntary psychiatric hold (i.e., 5150 in California) outside of the VA Facility, the following would occur:

1) Missed study visits – The Study Coordinator will follow study protocol on locating the participant and obtaining all the details for the missed visit, including any details from the hold.
2) The Study Coordinator will complete CRFs that were missed during the hold.
3) The participant will be asked to provide any documentation from the hold and asked to allow for permission to get records from the facility where the hold occurred using our Release of Information form.
4) The LSI may require additional documentation in addition to what is provided above, and those instances will be handled on a case-by-case basis.

Special Circumstances – Medical or Psychiatric Emergency Involving a Study Participant:

In the event that a study participant experiences a medical or psychiatric emergency during the course of their participation in CSP 590, the well-being of the participant will be the primary focus. Participating sites will follow their local practices for mental health or medical emergencies occurring during a study visit. Emergencies occurring outside of the study visit will also be handled according to local site practices with the well-being of the participant as the primary focus of the incident. Study procedures will continue or resume at a clinically appropriate time.

Special Circumstances – Incarceration:

Participants will be withdrawn upon discovery of an ongoing incarceration, and re-enrollment may be possible after release. Re-consent is required at the time of re-enrollment. If the incarceration occurred in the past when discovered, and no immediate future risk of incarceration is present, then continuation of participation is reasonable.

Neither the Safety Officer/Central Psychiatrist nor the local site research team will have control of study medication during a participant's incarceration. No new prescriptions for study medication will be written during the incarceration. No CRADO waiver is sought as we treat and document all incarcerations on VA Central IRB Form 119, Report of Serious Adverse Event (SAE) and Unanticipated Problem (UAP) Involving Risks to Participants or Others.

Special Circumstances – Participant Death:

If a participant dies while participating in the study, this will be treated as an early termination; however, as continuity of care and patient safety is no longer an issue, unblinding to the MH Provider will not occur.

Disclosure of study information under Special Circumstances: No information about participation in the study will be disclosed under any circumstances, unless required by law, in accordance with HIPAA authorization and Certificate of Confidentiality.

Notifications and Procedures in the Event of a Participant Death

Unblinding should never occur in the event of a participant death, given that:

1) The protocol states unblinding only occurs due to continuation of care at the warm hand-off at end of study
2) There are no impending safety issues posed to the participant after his or her death that would otherwise require unblinding

Release of information regarding study-related matters should never occur with any persons outside the study team, given that:

1) A Certificate of Confidentiality is in place for CSP 590. This protects participants' privacy by withholding information from anyone not connected with the conduct of the research study to avoid disclosure of information that may have adverse consequences. Because of this, the research team is not compelled in any Federal, State, or local civil, criminal administrative, legislative or other proceedings to provide information about the participant.
2) The HIPAA authorization form that participants sign at the beginning of the study protects their privacy and does not allow us to release information.
3) No written consent to disclosures is provided by the participant in conjunction with study participation.

See tables below for specific detail on Notifications and Procedures for Participant Deaths.

NOTIFICATIONS

Activity	Responsible Party	Considerations/ Requirements	Recommendation
Notification of Coordinating Center	Site Study Staff	Protocol	Reported via EDC system within 72 hours of the Site Investigator being made aware of the event. Email notification of the submission is relayed by the EDC system to the study Biostatistician, Clinical Research Pharmacist, Study Director and Study Chair.
Notification of CSPCC Study Staff and Director	Study Director, Clinical Research Pharmacist		
Notification of VA Central Office	CSPCRPCC, CSPCC	CSP SOP 3.6	Reported via email by Close of Business the next day after becoming aware of the event with a full report sent via email within 15 business days of the initial CO notification.
Notification of VA Central IRB	Site Study Staff, Chair's Office	CIRB Table of Reporting Requirements	-*If suicide*, expedited reporting is not required as this is an anticipated outcome. These SAEs are reported at continuing review. -*If "unanticipated *and* related" to research*, expedited reporting is required (within 5 business days of becoming aware of the occurrence). -*Otherwise* SAE is reported at continuing review.
Notification of Local Hospital Leadership	Site Study Staff	HIPAA, VHA Directive 1605.01, VHA Handbook 1200.05, Certificate of Confidentiality	**Remind local hospital leadership that release of information regarding study-related matters, including unblinding, with any persons outside the study team is prohibited.**
Disclosure of information about mental health care, *but not information about research participation*, to the family	Mental Health Provider (Note: this activity occurs outside of the study protocol, but is provided as a recommendation).	HIPAA, VHA Directive 1605.01, Certificate of Confidentiality	Local policies and procedures will vary. Consult Privacy Officer and other hospital leadership. Provide forms and assist family in completing the forms to facilitate their information seeking. **Do not provide any information regarding study-related matters, including unblinding, with any persons outside the study team.**

PROCEDURES

Activity	Responsible Party	Considerations/ Requirements	Recommendation
Completion of SAE forms	CSPCRPCC Study Staff	Protocol	Any other outstanding SAE forms should be closed out with the resolved option.
Completion of study forms	Site Study Staff	Protocol	Complete end of study form
Study visit entry into CPRS	Site Study Staff	Protocol, VHA Handbook 1200.05, Certificate of Confidentiality	-Include clinically relevant information (e.g., "participant expired") -Do not to include information about the study (e.g., "participant completed suicide") -Cause of death should be ascertained by medical records and/or death certificate (*should not* entered into CPRS, *should* be entered into DataLabs)

Determination of lithium levels: Close surveillance is essential to patient safety. This includes determination of lithium levels, renal function, thyroid function, hematological measures, electrolytes, and electrocardiograms (EKGs) and meticulous attention to concomitant drugs which might increase toxicity. Our protocol meets or exceeds published guidelines for monitoring patients on lithium.

QT Corrected (QTc) Interval: Due to potential lengthening of the QTc, all randomized participants will receive an electrocardiogram (EKG) on a minimum of four study time points:

1. at screening,
2. once during the titration phase,
3. once during steady state, and
4. at the end of study or early termination.

If the QTc is greater than or equal to 450 ms for men or 460 ms for women but less than 500 ms at any point during titration or during the subsequent course, the EKG will be repeated. If lengthened QTc_c is confirmed, Consultation with Study Cardiologist/Safety Officer and the Central Psychiatrist/Safety Officer will occur to develop an individualized plan for that patient. If after adjustment, the QTc remains prolonged, the subject's study drug will be held and the subject withdrawn from the study.

If the QTc interval rises above 450 ms (for males) or 460 ms (for females) this will report this as an AE to the appropriate committees and individuals.

If the QTc is equal to or greater than 500 ms at any point, the site will notify the CSPCC, CSPCRPCC, Central Psychiatrist/Safety Officer and Study Cardiologist/Safety Officer STAT. The participant will be terminated from the study and appropriate medical care will be provided.

Lithium levels will be determined according to the Titration Visits section (above) until steady state is achieved, then monthly until the end of the first six months of study participation, then quarterly.

To insure the highest quality, reliability, subject convenience, and timeliness of the lithium level determinations, all lithium level determinations will be made by a Central Lab.

By contract, lithium levels will be analyzed by a Central Lab and results will be uploaded to a database within 36 hours of receipt of sample by the Central Laboratory. Given that there could be delays in shipping and blood sample processing, the study will allow an additional 36 hours before requiring action i.e., consultation with the safety officer. The data will be accessible to the MAVERIC data coordinating center, which will calculate simulated lithium levels as described in XIII above. The results will be forwarded to the local site investigators as well as the Central Psychiatrist/Safety Officer.

Completion of the Study and Transfer of Care to Primary Providers

Patients who complete 1 year of study treatment

At the conclusion of the 1-year study treatment, participants will be referred to their treating mental health provider for continued management. There are data to suggest that suicidality and mood disturbances may be increased after stopping lithium. To insure continuity, the appointment with the subject's providers will be scheduled well before completion of the study. The Research Team will maintain responsibility for the subject until they have been seen by their treating clinician in a face-to-face encounter; the goal will be to provide warm-hand-offs through encounters that include the Research Team, the clinical provider, and the patient whenever possible. The research team will ensure that each study participant has a prescribing mental health provider assigned to him/her prior to study Month 10.

At the End of Study visit, the participant and the treating mental health provider will be informed of the treatment assignment. They will be reminded about the possible risks associated with rapid withdrawal of lithium and the need for a slow taper if lithium is to be discontinued. Patients will be asked to return for a 30-day follow-up study visit.

Patients who withdraw consent

Participants withdrawing consent will be asked to participate in a final study assessment. The blind will be broken at the time of this assessment and no further data will be collected. The Research Team will contact the participant's treating mental health provider to recommend gradual tapering of lithium as needed.

Patients who discontinue study treatment prior to 1 year

The investigator may discontinue the study medication for any reason, including adverse effects, safety concerns or protocol violations. In addition, participants may elect to discontinue study medication at any time. Discontinuation of study medication will not automatically result in withdrawal of the participant from the trial, nor unblind the study treatment. The investigators will encourage the participant to continue with study assessments but they will not be required to complete EKGs, blood draws or vital signs except for the 30 day follow-up visit (see Table 7). If a participant does not agree to continue assessments, the blind will be broken, to the participant's mental health provider, at the time they are tapered or discontinued. All ratings and assessments will be completed before the blind is broken.

When study medication is discontinued by the investigator or the patient opts for discontinuation, the investigator will ask the patient to return blister cards, study medication will be tapered gradually, and the facility's treating mental health providers will assume responsibility for further treatment.

Participants who prematurely discontinue treatment due to an adverse effect or other event will be evaluated 30 days after the last dose of study drug to complete the safety assessments.

Unblinding during treatment

A participant may be inadvertently or intentionally unblinded by medical personnel not involved with the study. A provider, for instance, may feel that it is medically necessary for the patient's treatment to determine a lithium level. This may occur even though participants will have flags in their electronic medical record indicating that they are enrolled in a research study

If and when the blind is broken, research and clinical ethics requires us to inform the participant of the assignment to lithium or placebo. This will not automatically result in withdrawal of the participant from the trial, and the participant will be included in all intention to treat (ITT) analyses.

See DTHP Section 11 for further information on emergency unblinding of a participant during the study.

Extended Follow-up

At the end of the study period, we will perform an electronic data sweep to collect passive follow-up data on lithium use and suicide related behaviors following active participation in the study for all subjects that had been randomized. In addition, death rates for individuals who were considered as part of pre-screening activities will be obtained by linking SSN with SPAN, BIRLS and the National Death Index. By the end of the 4 year study period, average follow-up including both active and passive follow up for the study subjects will be 2.5 years (first subject enrolled will have 4 years of follow up and last subject enrolled will have 1 year of follow up). However, subjects terminated from the protocol before they completed a full year of participation will have somewhat longer periods of passive follow-up. Data on lithium use and clinical and administrative data related to primary study endpoints over the extended observation period will be obtained by linking the study database to SPAN data, VA Electronic Medical Records data, VA Pharmacy Benefit Management data, the VA Beneficiary Identification and Records Locator System database, and the VA-DoD data repository for suicide-related data that will include data on causes of death from the National Death Index. Linkage for most variables will be through the VHA Corporate Data Warehouse, a national repository of data from VA Electronic Medical Records and several other VHA clinical and administrative systems. Hospital admission records and discharge summaries will be collected to determine if a subject was hospitalized to prevent suicide.

XV. MONITORING ADVERSE EVENTS

Role of the Site Investigator and Research Team in Adverse Event Monitoring

The site Research Team is responsible for the following:

1. Closely monitoring all subjects for new adverse events (AEs) and/or serious adverse events (SAEs);
2. Reviewing accuracy and completeness of all AEs and/or SAEs reports.

3. Complying with Cooperative Studies Program policies for reporting AEs and/or SAEs.
4. Complying with local Research & Development Committee (R&DC) policies for reporting AEs and/or Serious AEs.
5. Complying with:
    a. VA Central IRB (http://www.research.va.gov/vacentralirb/)
    b. VHA Handbook 1058.01 Research Reporting Compliance Requirements
6. Notifying VA Central IRB and local R&DC of safety issues reported to the investigator by the CSP.
7. Managing or reporting of adverse events or serious adverse event, and when questions arise, in consultation with the Site Physician, Clinical Research Pharmacist, Study Chair, or Study Director.

Definitions

For CSP#590, AE and SAEs will be collected using the International Conference on Harmonisation (ICH) Clinical Safety Data Management (ICH-E2A) and CSP Global Standard Operating Procedure (SOP) 3.6.2 definitions as follows:

Adverse Events: An AE is any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable and unintended event, including an abnormal laboratory finding, symptom, or disease associated with the research or the use of a medical investigational test article. An AE does not necessarily have to have a causal relationship with the research.

Serious Adverse Events: An SAE is an adverse event that results in:

- Death
- A life-threatening experience,
- Inpatient hospitalization
- Prolongation of hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or
- Requires medical, surgical, behavioral, social, or other intervention to prevent such an outcome.

Relatedness: Relatedness involves an assessment of the degree of causality between (or attributed to) the *study intervention* and the event. Site investigators are charged with making an assessment of relatedness based on their clinical judgment and experience. The assessment of relatedness provided by the site investigator is used by the sponsor (CSP) to determine if an AE/SAE represents an alteration or change in the safety profile of the study intervention. All AE/SAEs with a reasonable causal relationship to the investigative treatment may be considered "related". A definitive relationship does not need to be established.

Adverse Events and Serious Adverse Events Reporting Requirements

Adverse Events: Only adverse events possibly or definitely related to the study intervention will be reported. Documentation of this assessment may be recorded on a worksheet or source document. The lithium carbonate formulation used in CSP #590 is a commercially available product prescribed for bipolar disorder. Lithium has a well characterized adverse effect profile and there is no evidence suggesting this agent will demonstrate a different adverse event profile in CSP#590 from the one already known.

Serious Adverse Events: All SAEs shall be collected for CSP #590 regardless of relatedness; however, the Site Investigator must still make an assessment of whether or not the event is related to the study intervention. All SAEs will be recorded on the appropriate case report form. SAEs that meet the criteria for an endpoint should be reported as such.

Adverse Event and Serious Adverse Event Monitoring

Patients will be actively 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). Per CSP policy, active and passive monitoring of AEs and SAEs will begin when a participant signs the Randomization Informed Consent. Monitoring of AEs and SAEs will continue through to 30 days past the "end of study" for each study subject. (No SAEs should be collected for participants after withdrawal of consent).

Expedited Reporting of Serious Adverse Events to CSP

All SAEs will be promptly reported by reporting the event via the CSP #590 Electronic Data Capture (EDC) system ***within 72 hours*** of the Site Investigator or other study personnel being made aware of the event. Email notification of the submission is relayed by the EDC system to the study Biostatistician, Clinical Research Pharmacist, Study Director, and Study Chair. The CSP #590 Clinical Research Pharmacist (CRP) is responsible for evaluating all SAEs for immediate patient safety concerns. A back-up CRP will evaluate the event in if the primary CRP is not available.

Reporting of Serious Related and Unexpected Events

The determination of the expectedness of an event is the responsibility of the CSP. The source of information used in the determination of expectedness includes the CSP #590 Drug Information Report, the Informed Consent form, and published literature. SAEs determined by the CSP to be both related to the study intervention and unexpected after review by the CRP, the Study Chair, and consultants as needed will be reported to the VA Chief Research and Development Officer, the FDA, and site investigators.

Reporting of Adverse and Serious Adverse Events to the DMC

The Coordinating Center and CSPCRPCC will summarize blinded and unblinded AE and SAE data for the DMC in a format and on a schedule requested by the DMC. The DMC will receive results by treatment group (e.g. A versus B) but will not receive fully unblinded reports until all data collection has been completed.

Reporting Requirements of the VA Central IRB

Sites investigators are responsible for following the VA Central IRB policy in submitting safety data and protocol deviations as detailed in the VA Central IRBs' most recent policy including Table of Reporting Requirements, instructions, and forms (http://www.research.va.gov/vacentralirb/).

XVI. DATA MANAGEMENT AND DATA SECURITY PLANS

The MAVERIC CSPCC will manage the trial data using a web-based Electronic Data Capture (EDC) system. The EDC system allows direct entry of case report forms (CRF) into a web-based study database and thus allows site coordinators to manage their participants, handle data clarifications, and correct data online. This system makes patient data management easier, timelier, and more efficient. The electronic system will be used to create, modify, maintain and retrieve clinical data for CSP#590 during each step of the data collection process. The EDC system will be validated by the MAVERIC CSPCC Quality Assurance department to ensure the integrity of the data capture software.

Paper source documents will be provided to site coordinators as a primary means of collecting data. Data entered on paper CRFs will be used as source documentation for EDC entries. All paper-based study records will be kept under lock and key.

The Study Chair and Study Director will prepare an Operations Manual. A training session at the study kick-off meeting for all site investigators and site coordinators will be conducted to assure uniformity in patient management, data collection, and study procedures. At this training, site coordinators will be provided with reference materials on the software tool and tasks. Formal training on the use of the EDC system for clinical study management will also be conducted at investigator meetings and on an as-needed basis for new study personnel.

For CSP#590, EDC designers will create a specific database that includes case report forms, the interview schedule, and data queries. The purpose of data clarifications (DCFs) or data queries is to draw attention to data that are inconsistent or potentially erroneous. DCFs will be managed in two ways. Certain queries will be programmed into the forms that are designed to activate upon data entry if data is missing or discrepant with study parameters. Additional DCFs will be programmed using other data analysis tools such as SAS and will be uploaded into the system for study coordinators to address. Furthermore, the system will allow manual DCFs to be entered into the forms by the coordinating center as needed. Updates to the electronic forms and database can be generated during the study without impacting collected data. Study reports can be generated from exported data in order to track the study progress and to monitor adverse events, particularly Serious Adverse Events. Study reports will be circulated to appropriate individuals, including the Site Investigators, the Study Chair, the Study Director, and the DMC.

Study data is housed on secure VA servers, encrypted and protected in accordance with VA policies compliant with FDA requirements, Federal Information Security Management Act and the HIPAA Privacy and Security rules. MAVERIC CSPCC personnel manage the data access request process for the EDC system to ensure that data access is appropriate for each individual and the level of the individual access. VA's Office of Information & Technology (OI&T) is responsible for managing other VA system access and ensuring the security and integrity of VA information systems, including the databases and servers housing study data. In accordance with VA Handbooks and Directives, OI&T is responsible for ensuring that appropriate firewalls and data security is implemented and maintained, that data backups are performed and that data may be restored in the event of a system malfunction.

Hard copy data will be sent via a traceable mail system (i.e., FEDEX), via a courier, or via secure fax. Faxes are electronically routed to document management systems housed on VA protected servers located at the Regional Data Center in Philadelphia, PA. Access to these secure fax servers is restricted to the Coordinating Center personnel with approved access to the system. All secure fax servers are compliant with VA directive 1605.1 and 6500. All data security incidents will be reported in accordance with VA policy within one hour of discovering the incident to:

1. The District (local) Information Security Officer (ISO)
2. The MAVERIC CSPCC Quality Assurance department
3. The VA Central IRB

Study data will be coded and stored using a unique study identifier for each participant. Identifiable information will be collected for patient tracking and safety purposes, and kept in an encrypted, password protected file to which a small number of people will have access. Access to the cross-walk file linking the participant's identifiers and their study data will be restricted to the clinical site and to the approved personnel at the CSP coordinating center. This file will be destroyed according to CSP policy well after the close of the study.

Access to the study data is restricted to individuals with CSP approval. Individuals must be properly credentialed research staff and must be compliant with VA security trainings (e.g. HIPAA, Rules of Behavior, and Good Clinical Practices). Once formal training is completed, user accounts utilizing a URL specific to the study to access and use the system and enter patient data will be activated. Accounts will be password protected and unique to the each user. The account permissions will correspond with the users' functional study group (i.e., those for a site coordinator would differ from those of the coordinating center or site monitors). Furthermore, the permissions of the electronic systems are structured such that individual sites can only see the data for their study participants. They cannot see or access the data for another clinical site or for another participant. 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.

Access to protected health information (PHI) will be restricted to individuals approved by CSP to have access to the data.

At the Study Sites, between three and five FTE staff positions (depending on staffing allocations at each particular site) will have access to PHI. Individuals in these positions will be able to access all forms of PHI:

1. Site Investigator
2. Site Physician
3. Site Coordinator
4. Research Assistants (up to 2)

At the MAVERIC CSPCC nine staff positions will have access to all forms of PHI:

1. Center Director
2. Study Director
3. Project Manager/Project Coordinator
4. Data Manager
5. Primary Biostatistician
6. Secondary Biostatistician
7. Quality Assurance Officer
8. SAS Programmer
9. Research Assistant

At the CSPCRPCC four staff positions will have access to PHI. Individuals in these positions will be able to access de-identified forms of PHI:

1. Clinical Monitors
2. Study Pharmacist
3. Adverse Event Specialist (Regulatory Affairs and Safety Officer)
4. Pharmacy Project Manager

Periodic access control assessments will be made by Coordinating Center Quality Assurance personnel to verify that access is controlled and appropriate for personnel. In addition, the clinical monitors (SMART) will provide continuing education on good clinical practices compliance and will evaluate clinical site operations for violations of VA policies including VA data security policies and GCP.

At the end of the study, the data for CSP#590 will remain property of the Cooperative Studies Program and be stored and shared according to CSP guidelines and procedures. Retention and destruction of data will be conducted according to CSP operating procedures and federal and local VA regulations. This will include paper and electronic data stored at the study sites, the MAVERIC CSPCC, and at the VA facility housing our servers. Participating medical centers must retain study files and records after the study is completed in accordance with National Archives and Records Administration requirements as indicated in the VHA Records Control Schedule (at the time of this printing, such records must be held indefinitely until further notice). Research data forms are to be kept in accessible files for at least five years after the end of subject follow-up. These files can be retained for a longer period if required by applicable regulatory requirements or as agreed with an industry sponsor/partner, or if needed by the CSP. Identifiable data will be kept according to CSP policy as outlined in the "CSP Guidelines for the Planning and Conduct of Cooperative Studies".

XVII. QUALITY CONTROL PROCEDURES

A. Training on Study Measures

Prior to the initiation of the study, all site investigators and site coordinators will meet to review the governance and management of the study, study procedures and receive training on collecting data for the study. Much of this will take place during the study kickoff meeting. The protocol and case report forms will be sent to site investigators and coordinators to review prior to the meeting. During the meeting, study personnel will receive training on obtaining and maintaining source documents, and completing study assessments and case report forms. Verbal feedback and discussion will follow to ensure that each coordinator comprehends the proper methodology for assessment. This will include a training exercise to measure and maximize inter-rater reliability of clinical assessments. Any differences in the results will be discussed so that a consensus can be reached. The meeting will also cover an in-depth review of the study operations manual. Such a review will serve to reinforce the training described above and will orient the study personnel to the reference guides for the study.

During the study itself, we intend to maintain the highest inter and intra-reliability of the clinical assessment, especially the Columbia Suicide Severity Rating Scale (CSSRS) by having data collectors rate common simulated interviews on a monthly basis with feedback and discussion. Most of the other measures are self-reported.

B. Protocol deviations

Strict adherence to the protocol will be expected of every participating center and monitored by the DMC, the Executive Committee, and the Study Group. Any protocol violations will be fully documented on the Protocol Deviation form developed by the MAVERIC CSPCC. Protocol deviations will be summarized for review at each DMC meeting. Any medical center or participant with repeated protocol violations, and after remedial action, may be recommended for termination to the Director of the Cooperative Studies Program after discussion with the CSPCC Director, Study Chair, Executive Committee, and DMC. If any member of the DMC or of the monitoring bodies for CSP#590 feels that adherence to the protocol will be detrimental to a participant's health or well-being, the interest of the participant will take precedence and the subject withdrawn after consultation with the Executive Committee. Site coordinators will be responsible for reporting protocol deviations to the IRB of record as required.

C. Enrollment or Termination issues

I. Guidelines for Early Termination of a Study Site

During the course of a study, it may be necessary to drop one or more participating medical centers from the study. Such action must have the prior approval of the CSPCC Director and the Director of CSR&D. Early termination is usually based on recommendations from the Executive Committee and the Data Monitoring Committee and most often reflects inadequate patient intake

or serious noncompliance with Good Clinical Practices. This action should always be based on the best interests of the study and study participants and does not necessarily imply poor performance on the part of the site investigator or the medical center. Termination will be conducted per CSP guidelines and performance measures defined below.

II. Enrollment Issues and Site Performance Measures

The Study Chair and the study biostatistician will monitor the intake rate and operational aspects of the study. Participating medical centers will continue in the study only if adequate participant intake is maintained. The Executive Committee may take action leading to the discontinuation of enrollment at a center with the concurrence of the CSPCC Director. If recruitment is not proceeding at an appropriate rate, the Study Chair and study biostatistician will scrutinize the reasons for participant exclusions and other barriers to recruitment. Based on this information, the Executive Committee may choose, with the approval of the DMC and the Director, VA CSR&D, to drop centers, add additional centers, make minor modifications to the inclusion/exclusion criteria, or extend the recruitment period.

The following performance measures will be used to determine whether sites are at risk of being placed on probation or should be placed on probation.

1. Noncompliance with the protocol, ICH, or applicable federal regulations.

2. Recruitment rate: Recruitment rate will be calculated by dividing the number of randomized patients by the number of expected patients where the number of expected patients is based on prior SPAN and administrative data. This measure will be continuously monitored and sites between 75% and 90% of expected recruitment may be subject to remediation such as action plans or mentoring. Sites under 75% cumulative recruitment after a 3-month ramp-up period maybe recommended for probation. Assessment for probation will occur on a monthly basis.

3. Follow-up rate: Follow-up rate will be calculated by dividing the number of patients with follow-up forms completed by the expected number of patients with visits due. Both the numerator and denominator will be subject to a 4-week delay in order to allow for scheduling of visits and completion of forms. Sites with cumulative follow-up rates below 90% may be recommended for probation. Assessment for probation will occur on a monthly basis.

4. Forms completion rate: Forms completion rate will be calculated by dividing the number of completed forms by the number of expected forms, excluding forms marked "not collected". Forms completion rates will be calculated both by patient and by form. Sites with cumulative forms completion rates under 90% may be recommended for probation. Assessment for probation will occur on a monthly basis.

If a medical center is placed on probation, the Study Chair will confer with the site personnel and may visit the site, if necessary, to help improve the rate of recruitment. Once a site is placed on probation, failure to meet the requirements specified by the end of the probation period will result in a recommendation for termination. Additionally, sites that fail to meet two or more of

the above performance measures, and sites that habitually under-perform by any of these measures, will be at risk of termination.

To plan for the possible termination of a site(s) and the addition of a new site(s), back-up sites with IRB approval will be identified prior to study initiation to minimize the delay in adding a new site. The Executive Committee will take actions leading to discontinuation of a site only with the concurrence of the CSPCC Director. If a site is terminated from the trial, resources will be reallocated to other medical centers or used to start up a back-up site.

III. Premature Termination of the Study

The Director, CSP, can terminate a cooperative study before completion. The DMC makes recommendations as to whether the study should continue or be terminated. The decision to terminate a study prematurely is a complex one involving many factors. The DMC may consider the following circumstances as grounds for early termination:

1. If patient accrual falls far below that which is predicted (e.g., 75% of expected accrual), it will be necessary to reassess the study design and the potential value of its continuation.
2. If patient accrual far exceeds the predicted, this study could be completed at an earlier date.
3. If serious adverse events or mortality are noted to be excessive in either treatment group.
4. If interim analyses indicate a trend in the data which is unlikely to change prior to study completion.
5. If, during interim analyses on the primary end point, the significance level crosses the efficacy boundary established by the DMC.

Termination by recommendation of the DMC will be carried out as outlined in CSP guidelines.

XVIII. GOOD CLINICAL PRACTICES AND SITE REVIEW PROGRAM

Role of GCP

This trial will be conducted in compliance with Good Clinical Practice (GCP) regulations. The intent of these regulations is to safeguard subjects' welfare and assure the validity of data resulting from the clinical research. Study site personnel will receive GCP training at the study kickoff meeting. Subsequently, the VA Cooperative Studies Program will assist Site Investigators in complying with GCP requirements through its Site Monitoring, Auditing and Resource Team (SMART) based in Albuquerque, NM. SMART serves as the Quality Assurance arm of CSP for GCP compliance. SMART will assist study personnel in organizing study files and will be available throughout the trial to advise and assist Site Investigators regarding GCP issues. Further details of the SMART monitoring plan will be provided in the study-specific Operations Manual.

Summary of Monitoring and Auditing Plans:

Monitoring Visits

1. Initiation visits at each site soon after patient enrollment begins

2. Additional monitoring visits may be conducted as deemed necessary by study leadership or SMART.

Audits

1. Routine audits – independent site visits to one or more sites per year as determined by SMART.
2. For-Cause audits –independent audit of a site as requested by study leadership or CSP Central Office.
3. Audits may be scheduled or unannounced.

XIX. STUDY ORGANIZATION AND ADMINISTRATION

A. Administration

The administrative structure of this study is similar to others in CSP and includes:

The Cooperative Studies Program (VA Central Office) establishes overall policies and procedures that are applied to all VA cooperative studies through the Study Chair's office and the CSPCC.

The CSPCC and the **Study Chair's office** jointly will perform the day-to-day scientific and administrative coordination of the study. These include developing and revising the study protocol, Operations Manual, and case report forms; ensuring the appropriate support for the participating centers; scheduling meetings and conference calls; answering questions about the protocol; conducting site visits; publishing newsletters. The CSPCC will also prepare interim and final progress reports; and archive study data at the end of the study. Study progress reports will be produced every 6 months. Patient accrual, patient safety, and data quality will be monitored closely by the CSPCC to ensure that the study is progressing satisfactorily. Further delineation of responsibilities will be documented in communications with the Study Chair's office.

The Central Psychiatrist/Safety Officer will be an experienced VA-credentialed blinded psychiatrist responsible for reviewing clinical data from the sites and serving as a resource to sites for lithium dosing and other relevant clinical matters.

The **Study Cardiologist/Safety Officer** is a senior cardiologist with specialty in electrophysiologyand EKG interpretation

The CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC) manages the pharmaceutical aspects of multicenter pharmaceutical and device clinical trials including patient safety monitoring. CSPCRPCC acts as a liaison between the study participants, the FDA, and the manufacturers of the study drug(s) or device(s) in all VA Cooperative Studies that involve drugs or devices. The CSPCRPCC develops Drug Treatment and Handling Procedures, obtains and distributes the study drug(s), prepares a Drug Information Report for the study drug, and provides advice and consultation about drug-related matters during the study. CSPCRPCC is responsible for monitoring and reporting the safety of trial participants through the review, assessment, and communication of adverse events and serious adverse events reported by study

personnel with reviewing responsibilities occurring through ongoing communication with the Study Chair, Executive Committee, CSPCC, and CSP Central Office. The reporting activities include filing regulatory documents involving adverse events with the FDA and manufacturers to meet federal regulations and CSP policies. In conjunction with the CSPCC, the CSPCRPCC trends and analyzes safety data to prepare reports for various committees including the DMC, VA Central IRB (CIRB), Executive Committee(s), and Study Group meetings.

Each **participating VA medical center** will designate a site investigator (SI) to be responsible administratively and scientifically for the conduct of the study at the center. SIs will be expected to attend all annual Study Group meetings, as well as to hire and supervise personnel. By agreeing to participate in the study, the medical center delegates responsibility for global monitoring of the ongoing study to the DMC, the CSPCC Human Rights Committee, and the CSSEC.

The Cooperative Studies Scientific Evaluation Committee (CSSEC) reviews the scientific merit of all new cooperative study proposals and all ongoing cooperative studies every 3 years. The committee is composed of both VA and non-VA clinical research scientists, most of whom have had experience in managing their own cooperative studies.

The Study Group will be composed of the SIs from each participating center, the Study Chair, Study Director, and CSP staff (biostatistician, project manager, clinical research pharmacist, and others). The Study Chair will head the group, which will meet once a year to discuss the progress of the study, any problems that the investigators have encountered, and any suggestions for improving the study.

B. Monitoring

The following groups monitor the various aspects of the study. These committees will meet according to current Cooperative Studies Program guidelines. In addition, the CSP SMART will monitor the trial for GCP compliance as indicated above.

The Executive Committee is responsible for the operations of the study, including protocol amendments, and overall management of the study. It will be headed by the Study Chair and Study Director and consist of the study biostatistician, study project manager, clinical research pharmacist, CSP Center Director, selected participating investigators, and outside consultants as needed. This committee will meet regularly to review blinded data (not broken down by treatment group), decide upon changes in the study, determine the fate of hospitals whose performance is substandard, initiate any subprotocols, and discuss publication of the study results. This 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, including review of study participants with lithium levels of ≥ 1.3 to determine if there is an association with concomitant hypertensive medications and whether the participants' age or eGFR may play a role. Interim, independent, and unbiased reviews of the study's ongoing progress will be provided. The DMC will consist of experts in the study's subject matter field(s),

clinical trials, biostatistics, and ethics. These individuals 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 enrollment 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 regularly to the DMC for review. Unexpected, related 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 Study Director, and the study pharmacist. The study biostatistician will provide the appropriate data to the DMC at specified intervals for this purpose. Conditional power estimates may be provided to the DMC to assist them in making their decisions and recommendations at their request. To help them make their assessment, the Study Chair and study biostatistician will furnish the Data Monitoring Committee with appropriate monitoring data before each meeting. The DMC makes recommendations after each meeting to the Director of the Clinical Science Research and Development (CSRD) Service about whether the study should continue or be stopped.

The VA Central IRB will be the IRB of record for all VA sites. They will monitor the study's serious adverse events on a continual basis. They will conduct annual reviews of the study. In addition, some study materials (such as subject correspondence and protocol changes) will have to be reviewed by the VA CIRB, and approved prior to implementation.

The **CSPCC Human Rights Committee (HRC)** is composed primarily of lay people and is responsible for ensuring that patients' rights and safety are upheld prior to study initiation and during the conduct of the study. The committee reviews all new protocols, periodically makes site visits to participating centers to monitor firsthand the progress of the study, and may be asked to review any ethical and human rights issues that arise during the conduct of the study.

The **CSP Site Monitoring, Auditing and Resource Team (SMART)**, located at the CSPCRPCC in Albuquerque, will monitor the trial for compliance with Good Clinical Practices. GCP reviewers from SMART will visit participating sites shortly after enrollment is initiated and as needed thereafter to monitor investigator regulatory compliance, protocol adherence, and overall research practices. SMART 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 is required by the FDA, the frequency of follow-up monitoring visits will be based on the CSP standard for regulated trials. At a minimum, each site will be visited at least once during the study by SMART.

XX. PUBLICATIONS

Publication policy

It is the policy of the CSP that outcome data will not be revealed to the participating investigators until the data collection phase of the study is completed. This policy safeguards against possible biases affecting the data collection.

All presentations and publications from this study will be done in accordance with current CSP Guidelines, including the Authorship Policy. The most current version of the Guidelines should be referenced when planning any study publication.

The presentation or publication of any or all data collected by participating investigators on patients entered into the VA Cooperative Study is under the direct control of the study's Executive Committee. No individual participating investigator has any inherent right to perform analyses or interpretations or to make public presentations or seek publication of any or all of the data other than under the auspices and approval of the Executive Committee.

The Executive Committee has the authority to establish one or more publication subgroups of investigators and members of the Executive Committee for producing scientific presentations and publications. Authors with VA appointments must list their VA affiliation first. The VA contributions to the research project should be acknowledged in all written and oral presentations of the research results, including scientific articles, news releases, news conferences, public lectures, and media interviews.

All study reports and journal manuscripts must be reviewed and approved by the MAVERIC CSPCC Director prior to submission for publication. After approval for submission is granted by the MAVERIC CSPCC Director, VA Central Office must be notified upon acceptance of any publications. This includes minor publications such as abstracts and poster presentations.

Planned Publications

A list of planned publications is provided below. The design paper will be completed during the conduct of the study. The manuscript detailing the main study results will be completed within six months of the study's completion.

1. Efficacy of lithium in the prevention of repeated suicide attempts in high risk subjects with affective disorders: A VA Cooperative Study (main publication that will present clinical outcomes)
2. Design, rationale and methodological challenges in a randomized placebo-controlled trial of lithium and enhanced usual care of persons with recent suicide attempts.
3. Determinants of treatment adherence to lithium in participants who recently attempted suicide.
4. Predictors of impulsive and non-impulsive suicide attempts. (Secondary aim b).
5. Predictors of repeated suicide attempts and suicide events (secondary aim c and d).

6. Effect of adjunctive lithium in managing symptoms of bipolar disorder and depression in patients who have survived a suicide attempt (secondary aim e)
7. Mediators and moderators of lithium augmentation on prevention of suicide reattempts (secondary aims b,f)
8. Relationship between lithium plasma levels and repeated suicide attempts in patients who have survived a suicide attempt

XXI. TABLES AND FIGURES

Table 1: Instruments and scales for data acquisition

Domain	Measure	Abbreviation	Description	Source	# items	Study Purpose	Time (minutes)
Suicidality	Columbia Suicide Severity Rating Scale-lifetime version, supplemented (Posner et al., 2011; Matarazzo et al., 2013)	CSSRS-lifetime-supp	History of suicide-related behaviors	Interview	39 (6 item screen)	Eligibility	20
	Columbia Scale -since last visit version, supplemented (Posner et al., 2011; Matarazzo et al., 2013)	CSSRS-last visit-supp	Interim history of suicide related behaviors	Interview	Variable (6 item screen)	Monitoring	10
	Suicide Intent Scale (Beck et al., 1974)	SIS	Context and characteristics of suicide attempts	Interview	15	Monitoring	8
Psychiatric Diagnosis	Mini-International Neuropsychiatric Interview (Sheehan et al., 1998)	MINI	Structured interview to elicit psychiatric symptoms and determine diagnoses	Interview	Variable	Eligibility	20
	PTSD Checklist (modified to allow DSM-IV-TR and DSM-5 diagnoses); Blanchard et al., 1996)	PCL	Self-rating scale to be administered as a structured interview	Self or Interview	22	Potential covariate for exploratory analyses	6
	Substance use disorders module from Structured Clinical Interview for DSM-IV-TR Axis 1 Disorders (First et al., 2002)	SCID SUD	Supplementary questions related to substance use diagnoses	Interview	Variable	Eligibility	10
Cognition and Decision-Making Capacity	Orientation Memory Concentration Test (Katzman et al., 1983)	OMC	Cognitive screening instrument	Interview	6	Eligibility	6
	The Jeste Decision-Making Capacity Assessment – University of California, San Diego Brief Assessment of Capacity to Consent (UBACC)	UBACC	Evaluation of decision-making capacity	Interview	Variable	Eligibility	5

Mental Health Symptoms	Patient Health Questionaire-9 (Kroenke et al., 2001)	PHQ-9	Symptoms of depression	Self or Interview	10	Secondary Outcome	7.5
	Internal State Scale (Bauer et al., 2000)	ISS	Symptoms of bipolar disorder	Self or Interview	15	Secondary Outcome	7.5
	Alcohol Use Disorders Identification Test-C (Bradley et al., 2007)	Audit C	Quantity-frequency data on alcohol use	Interview	3	Secondary Outcome	3
Moderators	Buss-Perry Aggression Scale (Buss & Perry, 1992)	Buss Perry	Aggression as a trait	Self	29	Secondary Outcome	10
	Barratt Impulsiveness Scale (Patton et al., 1995)	Barratt	Impulsivity as a trait	Self	30	Secondary Outcome	10
Lithium side effects	Lithium side effects checklist		Systematic review of possible lithium side effects	Interview	8	Monitoring	5
Use of VA and non-VA health and mental health services Sirey et al., 2005)	Self-report log based on the Cornell Services Index (Sirey et al.,2005)		Use of health and mental health services to include patient's report of reasons for hospitalization or emergency department visits	Log maintained by subject and reviewed by research staff at each visit	Variable	Monitoring	5 minutes for review

Table 2: Comparison of select prior studies of lithium with CSP590

	Cipriani (2005)	Guzzetta (2007)	Goodwin (2003)	Lauterbach (2008)	Oquendo (2011)	Proposed CSP590
Design	Meta-analysis of 32 RCTs conducted to evaluate other outcomes	Meta-analysis of 8 studies	Observational study in two health plans	RCT (Terminated prematurely due to low recruitment)	RCT (Terminated prematurely due to low recruitment)	Randomized Clinical Trial
Period	1968-2002	1976-2006	1994-2001	2001-2006	2000-2007	Prospective
Study Population	Mood Disorder	Major Depressive Disorder	Bipolar Disorder	76% Major Depressive Disorder, 22% Other	Bipolar Disorder	Bipolar and Major Depression
Treatment s	lithium vs. other agents	lithium vs. other agents	lithium vs. divalproex or carbamezapine	lithium vs. placebo	lithium vs. valproate	lithium vs. placebo
Sample Size	2458 (1389 lithium, 2069 other agents)	252 lithium, 205 other, 128 Crossover	> 23000 (16020 li, 10669 valproate, 2516 carbamazepine)	167 (84 lithium, 83 placebo)	98 (49 lithium, 49 valproate)	1862
No. of Years followed-up	Varies across studies	Li, 4.6, Other, 6.7	2.9	1	1.35 Li, 1.5 valproate	1
Average Age (yrs)	Varies across studies	Varies across studies	38	39	33.5	~ 44.6
% male	Varies across studies	Varies across studies	35%	42%	28%	~ 86%
Attrition	Varies across studies	Varies across studies	NA	Overall: 58% lithium, 59% placebo Tx related: 21% lithium, 6% placebo	Overall: 50% lithium, 53% valproate Tx related: 11% lithium, 13% valproate	~ 20% Tx related; 40% non-Tx related

Outcomes considered	Suicides, Suicides + deliberate self-directed violence, all cause mortality	Suicides, Suicidal behavior	Suicide, Attempts w ED visit or hospitalization	Suicide reattempt within 1 year after index attempt	Suicide attempt or suicide event including attempt/ hospitalization/ change in medication in response to suicide plans.	Suicide attempts, interrupted attempts, hospitalizations to prevent suicide, and deaths from suicide
Observed Event Rates	For suicide, 2/503 for lithium vs. 11/602 for other. For suicide +deliberate self-directed violence, 2/670 for lithium vs. 18/781 for other. For all cause mortality, 9/696 for lithium vs. 22/788 for other	For suicide, 0.33% for lithium vs. 2.22% for other. For suicide behaviors, 2/252 for lithium vs. 19/205 for other	For suicide 9/13597 for lithium, 14/8297 for valproate, 2/2036 for carbamazepine. For attempts. 67/16020 for lithium, 112/10669 for valproate, 39/2516 for carbamazepine)	Lithium: 7/84 (8.3%), placebo: 10/83 (12%)	Lithium: 6/49 (12.2%), valproate: 8/49 (16.3%) for suicide attempts over 2 year period. At one year, 82% survival and 88% survival in valproate and lithium groups respectively.	~ 15% rate for Reattempts, interrupted attempts, hospitalizations to prevent suicide, and deaths from suicide
Observed Effects	74% reduction for suicide, 79% for suicide + deliberate self-directed violence, 58% for all cause mortality	85% reduction for suicide, 88.5% for suicidal behavior	60% reduction in suicides, 41-44% for attempts	Adjusted reduction of 48%. Not significant.	One Year reduction estimated as 33%. Not significant	~ 37% reduction in repeated attempts, interrupted attempts, hospitalizations to prevent suicide, and deaths from suicide

Table 3: Evaluation of variability in Statistical Power assuming 5% Overall Type I error.

(a) Change in statistical power for fixed sample size and a range of effect sizes

		Event Rates				
Evaluable N	N per arm	Placebo	Active	#Events	Effect	Power
1490	745	15%	11%	190	30%	73%
1490	745	15%	10%	188	31%	77%
1490	745	15%	10%	187	33%	81%
1490	745	15%	10%	185	35%	85%
***1490**	**745**	**15%**	**9.5%**	**182**	**37%**	**90%**
1490	745	15%	9%	179	40%	94%

(b) Change in statistical power for fixed effect size and a range of sample sizes

	Event Rates					
Effect	Placebo	Active	Evaluable N	N per arm	#Events	Power
37%	15%	9.5%	1700	850	208	93%
***37%**	**15%**	**9.5%**	**1490**	**745**	**182**	**90%**
37%	15%	9.5%	1400	700	171	88%
37%	15%	9.5%	1200	600	147	83%
37%	15%	9.5%	1100	550	134	79%
37%	15%	9.5%	1000	500	122	75%

(c) Change in statistical power for fixed effect and sample size and a range of event rates

		Event Rates				
Total N	N per arm	Placebo	Active	#Events	Effect	Power
***1490**	**745**	**15%**	**9.5%**	**182**	**37%**	**90%**
1490	745	14%	8.8%	170	37%	88%
1490	745	13%	8.2%	158	37%	85%
1490	745	12%	7.6%	146	37%	82%
1490	745	11%	6.9%	134	37%	78%
1490	745	10%	6.3%	121	37%	73%

*Highlight indicates parameters proposed in CSP590

Table 4. Potentially eligible subjects for 1-year period by site

Site#	Facility	Count	Cumulative	Site#	Facility	Count	Cumulative
1	Orlando	249	249	26	Northern Calif	101	3660
2	San Diego	218	467	27	Montana	99	3759
3	Atlanta	214	681	28	Central Texas	97	3856
4	Las Vegas	204	885	29	Baltimore, includes Perry Point	96	3952
5	Marion, Illinois	185	1070	30	Edward Hines VAMC	96	4048
6	West Palm Beach	166	1236	31	Palo Alto	95	4143
7	Denver	160	1396	32	Central Arkansas	93	4236
8	Milwaukee	156	1552	33	Salt Lake City	83	4319
9	Central Alabama	155	1707	34	Muskogee	80	4399
10	Puget Sound HCS	149	1856	35	Philadelphia	79	4478
11	Madison	130	1986	36	Roseburg	79	4557
12	Washington DC	123	2109	37	Marion, IN	78	4635
13	St Louis	122	2231	38	Columbia, SC	78	4713
14	Tampa	122	2353	39	Pittsburgh	78	4791
15	Houston	115	2468	40	Reno	78	4869
16	Gainesville	115	2583	41	Tenn. Valley	77	4946
17	Phoenix	114	2697	42	Portland	76	5022
18	Minneapolis	113	2810	43	Mountain Home	74	5096
19	Jesse Brown VAMC	111	2921	44	West Texas	71	5167
20	Amarillo	110	3031	45	New Jersey	71	5238
21	Dallas	108	3139	46	Tomah	69	5307
22	Tucson	107	3246	47	Battle Creek	66	5373
23	Indianapolis	106	3352	48	Bay Pines	66	5439
24	Dublin	105	3457	49	Poplar Bluff	64	5503
25	Biloxi	102	3559	50	Loma Linda	64	5567

Table 5: Medications with potential interactions with lithium

Increased risk of CNS side effects/toxicity
- Carbamazepine
- Calcium channel blockers
- Haloperidol
- Serotonin Re-uptake Inhibitors
- Serotonin modulators
- Tricyclic antidepressants

Decreased thyroid function
- Extended use of iodide preparations

Lower lithium levels
- Acetazolamide
- Aminophylline
- Caffeine
- Theophylline
- Alkalinizing agents such as sodium bicarbonate

Increase lithium levels
- Diuretics
- Angiotensin converting enzyme (ACE) inhibitors
- Angiotensin II Receptor Antagonists
- Calcium channel blockers (non-dihydropyridine)
- Metronidazole
- Non-steroidal Anti-inflammatory agents (including COX-2 inhibitors)
- MAO Inhibitors

May increase or decrease lithium levels
- Fluoxetine

Unstated, Other, or mixed
- Alpha-methyl DOPA (Aldomet)
- Antipsychotic agents (typical and atypical)

Table 6: Study Flowchart for Participants on Study Medication

	Screening	Study Entry		Study Participation with Assigned Treatment										Termination	
				Titration				Steady State							
Study Activities	Eligibility Evaluation (ICF 1)	Confirming Eligibility (ICF 2)	BL	T 1	T 2-3	T 4	T 5-6	M 2-5	M 6	M 7-8	M 9	M10,11	Early D/C	End of Study	F/U (30 days)
Estimated time per visit	2 hrs	2 hrs	1.25hrs	1hr	45min	1.25hr	45min	1hr	1.25hr	1hr	1hr	1hr	1.75hr	1.75hr	30min
Phone contact allowed[+]								Yes		Yes		Yes			Yes
Eligibility Screening															
Informed Consent[++]	X	X													
Review Incl/Excl. Criteria (S12)	X	X													
Demog. and military history (B02, B03)		X													
Medical history reviewed (B04)			X												
Psychiatric history reviewed (S01)	X		X												
Medications and treatments reviewed (S03)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MH Provider concurrence documentation obtained	X	(X)													
Primary Care Provider awareness documentation obtained[+++]	X	(X)													
Medical Assessments															
Physical Exam (B01)		X											X	X	
Vital Signs (B01, T04)		X	X	X	X	X	X	X	X	X	X	X	X	X	
EKG[++++] (S09)		X		X (once during titration)				X (once during steady state)					X	X	
Creatinine (S10, T02)		X		X	X	X	X	X	X		X		X	X	
CBC, electrolytes, calcium (S10, T01)		X				X			X				X	X	
TSH, T4 (S10, T02)		X				X			X				X	X	
Pregnancy test as appropriate (S10, T01)		X	X	X	X	X	X	X	X	X	X	X	X	X	
Interim history (B05)			X	X	X	X	X	X	X	X	X	X	X	X	X
Enrollment															

Randomization (S12)			X												

Study Medication	Eligibility Evaluation	Eligibility Confirmation	BL	T 1	T 2-3	T 4	T 5-6	M 2-5*	M 6	M 7-8	M 9	M 10-11	Early D/C	End of Study	F/U (30 days)
Lithium level (T02)				X	X	X	X	X	X		X				
Adherence (T03, T05)				X	X	X	X	X	X	X	X	X	X	X	
Adverse events, (SAEs and AEs) (using lithium side effects checklist) (B13, T02)			X	X	X	X	X	X	X	X	X	X	X	X	X
Planned dose adjustment				X	X	X	X								
Dispense study medication[+++++]			X	X	X	X	X	X	X	X	X	X	(X)	(X)	
Current Treatment Info.															
Medications (S03)	X		X	X	X	X	X	X	X	X	X	X	X	X	
VA record review	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Service use based on the Cornell Service Index (B05)			X	X	X	X	X	X	X	X	X	X	X	X	X
Psychiatric Measures															
MINI (S11)	X														
PCL (B12)		X													
SCID SUD (S05)	X														
OMC (S06)	X														
UBACC (S04)	X														
CSSRS-lifetime version suppl with SIS for index attempt (S07, S08)	X														
CSSRS-last visit version supple with SIS f/u for attempts (B06, S08)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PHQ-9 (B07)			X	X		X		X	X	X	X	X	X	X	X
ISS (B08)			X	X		X		X	X	X	X	X	X	X	X
Audit C (B09)			X	X				Month 3	X		X		X	X	
Buss-Perry (B10)			X												

Barratt (B11)			X												

+ During months 2-5, if participants have completed titration procedures, participant's visits may be conducted over the phone at alternating time points (e.g. Months 2 and 4, or Months 3 and 5 visits can be over the phone. Visits done by phone will not have VS collected. The same is true of months 7-8 and months 10-11. The exception to this is for participants of childbearing potential who will need to be seen in-person for all study visits because a pregnancy test needs to be administered.
++ Participants will provide informed consent in two stages – consent for screening evaluation (ICF1), followed by consent for main study (ICF2) if eligible (see consent forms)
+++ The mental health provider must provide concurrence after ICF 1 has been signed and prior to randomization. The primary care provider must be made aware of study participation prior to randomization.
++++ EKG will be performed on all participants at screening, at least once during titration and once when steady state has been achieved and at End of Study/Early Termination
+++++ Study medication is only dispensed at end of study visits if a warm-hand off has been delayed.

Table 7: Study Flowchart for Participants Who Discontinue Study Medication

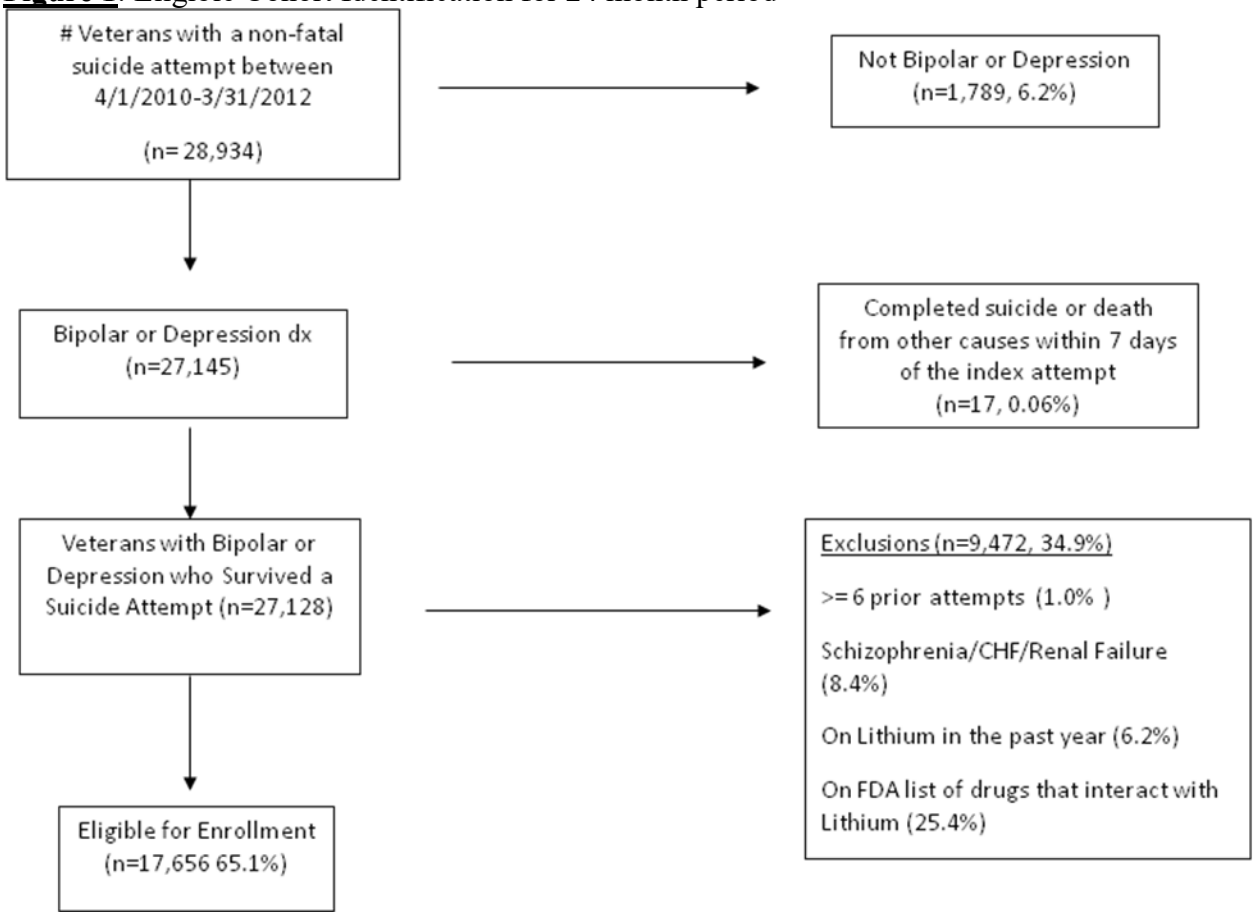
	DISCONTINUE STUDY MEDICATION **WITHOUT ACTIVE FOLLOW UP**		DISCONTINUE STUDY MEDICATION **WITH ACTIVE FOLLOW UP**				
Study Activities	At Early D/C Visit	At 30 Days F/U Visit	AT EARLY D/C VISIT	AT 30 DAYS F/U VISIT	DURING ACTIVE FOLLOW UP*	AT END OF STUDY VISIT	AT 30 DAYS F/U VISIT
Physical Exam (B01)	X		X				
Medications and treatments reviewed (S03)	X		X		X	X	
Vital Signs (B01, T04)**	X		X	X			
EKG (S09)	X		X				
Creatinine (S10, T02)	X		X				
CBC, electrolytes, calcium (S10, T01)	X		X				
TSH, T4 (S10, T02)	X		X				
Pregnancy test as appropriate (S10, T01)	X		X				
Service use based on the Cornell Service Index (B05)	X	X	X	X	X	X	X
Lithium level (T02)							
Adherence (T03, T05)	X		X				
Adverse events, (SAEs and AEs) (using lithium side effects checklist) (B13, T02)	X	X	X	X	X	X	X

Medications (S03)	X		X		X	X	
VA record review	X	X	X	X	X	X	X
SIS (S08)	X (as needed)	X (as needed)	X (as needed)	X (as needed)	X (as needed)	X (as needed)	X (as needed)
Columbia Follow up (B06)	X	X	X	X	X	X	X
PHG-9 (B07)	X	X	X	X	X	X	X
ISS (B08)	X	X	X	X	X	X	X
Audit C (B09)	X		X			X	
Follow up laboratory Information (T01)	X		X				
Participant visit overview (T02)	X		X				
Outcome Adjudication (B17)	X (as needed)	X (as needed)	X (as needed)	X (as needed)	X (as needed)	X (as needed)	X (as needed)
Narrative for Outcome Adjudication (B18)	X (as needed)	X (as needed)	X (as needed)	X (as needed)	X (as needed)	X (as needed)	X (as needed)
End of Study (Form E)	X		X			X	

*During months 2-5 participant's visits may be conducted over the phone at alternating time points (e.g. Months 2 and 4, or Months 3 and 5 visits) can be over the phone. Visits done by phone will not have VS collected. The same is true of months 7-8 and months 10-11.

** Vital signs will be collected for all participants at Early D/C. Additionally, participants that remain in active follow-up will have vitals signs collected at their 30 day follow-up visits.

Figure 1: Eligible Cohort Identification for 24 month period



XXII. REFERENCES

Abou-Auda HS, AL-Yamani MJ, Abou_Shabaan RR, Khoshhal SI. A new accurate method for predicting lithium clearance and daily dosage requirements in adult psychiatric patients. Bipolar Disorder 10:369-376, 2008.

Aggarwal SP, et al. Clinical trial testing lithium in ALS terminates early for futility. Lancet Neurology 9.5: 481, 2010.

Ahearn EP, Chen P, Hertzberg M, Cornette M, Suvalsky L, Cooley-Olson D, Swanlund J, Eickhoff J, Becker T, Krahn D. Suicide Attempts in Veterans with Bipolar Disorder During Treatment with Lithium, Divalproex, and Atypical Antipsychotics. Journal of Affective Disorders, in press.

Ahrens B, Grof P, Moller HJ, Muller-Oerlinghausen B, Wolf T. Extended survival of patients on long-term lithium treatment. Can J Psychiatry. 40:241-6, 1995.

Ahrens B, Muller-Oerlinghausen B, Grof P. Length of lithium treatment needed to eliminate the high mortality of affective disorders. Br J Psychiatry Suppl. 27-9, 1993.

Ahrens B, Muller-Oerlinghausen B, Schou M, et al. Excess cardiovascular and suicide mortality of affective disorders may be reduced by lithium prophylaxis. J Affect Disord. 33:67-75, 1995.

Ahrens B. Muller-Oerlinghausen B. Does lithium exert an independent antisuicidal effect? Pharmacopsychiatry. 34:132-6, 2001.

Amado I, et al. Effects of Lithium on Saccadic Eye Movements in Healthy Subjects in a Ten-Day Double-Blind Placebo-Controlled Cross-Over Pilot Study. Pharmacopsychiatry 38.06: 321-325, 2005.

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), Arlington, VA, American Psychiatric Association, 2000.

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), Arlington, VA, American Psychiatric Association, 2013.

American Psychiatric Association: Practice guideline for the treatment of patients with bipolar disorder (revision). Am J Psychiatry 2002; 159:1–50.

APA Work Group on Assessment and Treatment of Patients With Suicidal Behaviors. Assessment and Treatment of Patients With Suicidal Behaviors. American Psychiatric Association, Arlington, VA, 2003

BALANCE investigators and collaborators. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet 375: 385-395, 2010.

Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J.Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. Bipolar Disord 8: 625–39, 2006.

Baldessarini RJ, Tondo L, Hennen J. Effects of lithium treatment and its discontinuation on suicidal behavior in bipolar manic-depressive disorders. J Clin Psychiatry. 60 Suppl 2:77-84, 1999.

Baldessarini RJ, Tondo L, Hennen J. Treating the suicidal patient with bipolar disorder. Reducing suicide risk with lithium. Ann N Y Acad Sci. 932:24-38, 2001

Baldessarini RJ, Tondo L, Hennen J: Lithium treatment and suicide risk in major affective disorders: update and new findings. J Clin Psychiatry 64(suppl 5):44–52, 2003

Baldessarini RJ, Tondo L, Viguera AC. Discontinuing lithium maintenance treatment in bipolar disorders: risks and implications. Bipolar Disord. 1:17-24, 1999.

Bauer M, Dopfmer S: Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. J Clin Psychopharmacol 19:427–434, 1999

Bauer M. Forsthoff A. Baethge C,. Adli M, . Berghofer A, et al. Lithium augmentation therapy in refractory depression-update 2002. European Archives of Psychiatry & Clinical Neuroscience. 253:132-9, 2003.

Bauer M, et al. Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. American Journal of Psychiatry 157: 1429-1435, 2000.

Bauer MS, Vojta, Kinosian B, Altschuler L, Glick H. The Internal State Scale: replication of its discriminating ability in a multisite public sector sample. Bipolar Disorders 2: 340-6, 2000.

Beck AT,Schuyler D, Herman I. Development of suicidal intent scales in AT Beck, HLP Resnik, DJ Lettieri (Eds.), The Prediction of Suicide, Charles Press, Philadelphia, PA, 1974, pp. 45–56.

Bell EC, et al. Lithium and valproate attenuate dextroamphetamine-induced changes in brain activation. Human Psychopharmacology: Clinical and Experimental 20: 87-96, 2005.

Bell EC, et al. Differential effects of chronic lithium and valproate on brain activation in healthy volunteers. Human Psychopharmacology: Clinical and Experimental 20: 415-424, 2005.

Bergen H, Hawton K, Kapur N, Cooper J, Steeg S, Ness J, Waters K. Shared characteristics of suicides and other unnatural deaths following non-fatal self-harm. A multicentre study of risk factors. Psychological Medicine. 42:727-41, 2012.

Blanchard, EB, Jones-Alexander J, Buckley TC, Forneris CA. Psychometric properties of the PTSD checklist (PCL). Behavioral Research and Therapy, 23, 669-673, 1996.

Bossarte R. Report to the Under Secretary. Veterans Health Administration. January, 2013

Bowden C, Fawcett J: Pharmacotherapy and risk of suicidal behaviors among patients with bipolar disorder (letter). JAMA 291:939, 2004

Bowden CL, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. Archives of General Psychiatry 60: 392-400, 2003.

Bowden CL., et al. Relationship of mania symptomatology to maintenance treatment response with divalproex, lithium, or placebo. Neuropsychopharmacology 30: 1932-1939, 2005.

Bowden CL, et al. A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. Journal of Clinical Psychiatry 66: 111-121, 2005.

Bowden CL, et al. Impact of lamotrigine and lithium on weight in obese and nonobese patients with bipolar I disorder. American Journal of Psychiatry 163: 1199-1201, 2006.

Bradley KA, DeBenedetti AF, Volk RJ, Williams EC, Frandk D, Kivlahan DR. AUDIT-C as a brief screen for alcohol misuse in primary care. Alcohol Clin Exp Res 31: 1208-1217, 2007

Brent DA, Johnson BA, Perper J, Connolly J, Bridge J, et al. Personality disorder, personality traits, impulsive violence, and completed suicide in adolescents. J. Am. Acad. Child Adolesc. Psychiatry 33:1080–86, 1994.

Brodersen A, Licht RW, Vestergaard P, Olesen AV, Mortensen PB. [Mortality in patients with affective disorder who commenced treatment with lithium. A 16-year follow-up]. Ugeskr Laeger.163, :6428-32, 2001.

Brodersen A, Licht RW, Vestergaard P, Olesen AV, Mortensen PB. Sixteen-year mortality in patients with affective disorder commenced on lithium. Br J Psychiatry. 176:429-33, 2000.

Brodsky BS, Oquendo M, Ellis SP, Haas GL, Malone KM,Mann JJ. The relationship of childhood abuse to impulsivity and suicidal behavior in adults with major depression. Am. J. Psychiatry 158:1871–77, 2001

Brown GK, Holloway MG. Suicide attempt report template. Unpublished document. University of Pennsylvania, 2005.

Brown GK. Ten Have T. Henriques GR. Xie SX. Hollander JE. Beck AT. Cognitive therapy for the prevention of suicide attempts: a randomized controlled trial. JAMA. 294:563-70, 2005.

Burgess SSA,Geddes J,Hawton KKE, TaylorMJ, Townsend E, Jamison K, Goodwin G. Lithium for maintenance treatment of mood disorders. Cochrane Database of Systematic Reviews Art.No.: CD003013. DOI: 10.1002/14651858.CD003013, 2001.

Buss AH, Perry MP. The aggression questionnaire. Journal of Personality and Social Psychology, 63, 452-459, 1992.

Calabrese JR, et al. Recurrence in bipolar I disorder: a post hoc analysis excluding relapses in two double-blind maintenance studies. Biological Psychiatry 59: 1061-1064, 2006.

Campbell M, Adams PB, Small AM, Kafantaris V, Silva RR, et al. Lithium in hospitalized aggressive children with conduct disorder: a double-blind and placebo-controlled study. J. Am. Acad. Child Adolesc Psychiatry 34:445–53, 1995.

Campbell M, Small AM, Green WH, Jennings SJ, Perry R, et al. Behavioral efficacy of haloperidol and lithium carbonate. A comparison in hospitalized aggressive children with conduct disorder. Arch. Gen. Psychiatry 41:650–56, 1984

Cipriani A, Pretty H, Hawton K, Geddes JR. Lithium in the Prevention of Suicidal Behavior and All- Cause Mortality in Patients With Mood Disorders: A Systematic Review of Randomized Trials Am J Psychiatry 162:1805–1819, 2005

Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the Prevention of Suicide in Mood Disorders: Updated Systematic Review and Meta-Analysis. BMJ 246:f3646, 2013.

Collins JC , McFarland BH: Divalproex, lithium, and suicide among Medicaid patients with bipolar disorder. J Affect Disord 107:23–28, 2008.

Cooper J, Kapur N, Webb R, Lawlor M, Guthrie E, Mackway-Jones K, Appleby L Suicide after deliberate self-harm : a 4-year cohort study. American Journal of Psychiatry 162, 297–303, 2005.

Coppen A, Bailey J, Houston G, Silcocks P. Lithium and mortality: a 15 year follow-up. Clin Neuropharmacol. 15 Suppl 1 Pt A:448A-449A, 1992.

Coppen A, Farmer R. Suicide mortality in patients on lithium maintenance therapy. J Affect Disord. 50:261-7, 1998.

Coppen A. Lithium in unipolar depression and the prevention of suicide. J Clin Psychiatry. 61 Suppl 9:52-6, 2000.

Coryell W, Arndt S, Turvey C, Endicott J, Solomon D, et al. Lithium and suicidal behavior in major affective disorder: a case–control study. Acta Psychiatr Scand 104: 193–197, 2001.

Crosby AE, Ortega L, Melanson C. Self-directed Violence Surveillance: Uniform Definitions and Recommended Data Elements, Verion 1.0, Centers for Disease Control and Prevention, National Center for Injury Prevention and Control: 2011.

Department of Veterans Affairs, Department of Defense. VA/DoD clinical practice guideline for management of major depressive disorder (MDD). Washington (DC): Department of Veteran Affairs, Department of Defense; 2009.

Department of Veterans Affairs, Department of Defense. VA/DoD clinical practice guideline for the assessment and management of patients at risk for suicide. Washington (DS): Department of Veterans Affairs, Department of Defense, 2013.

Department of Veterans Affairs. Veterans Health Administration. VHA Directive 2008-036. Use of patient Record Flags to Identify Patients at High Risk for Suicide. Washington, DC, July 18, 2008

Deputy Under Secretary for Health for Operations and Management. Memorandum. Standardized Suicide Nomenclature (Self-Directed Violence Classification System), Washington, DC. April 19, 2010.

Dolgin E. The ultimate endpoint. Nature Medicine 18: 190-193, 2012.

Dougherty DM, Mathias CW, Marsh DM,Papageorgiou TD, Swann AC, Moeller FG. Laboratory measured behavioral impulsivity relates to suicide attempt history. Suicide Life Threat. Behav. 34:374–85, 2004.

DSM-IVTR American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.). Washington, DC, 2000

Dunner DL. Correlates of suicidal behavior and lithium treatment in bipolar disorder. J Clin Psychiatry. 65 Suppl 10:5-10, 2004.

Ellis TE. Green KL. Allen JG. Jobes DA. Nadorff MR. Collaborative assessment and management of suicidality in an inpatient setting: results of a pilot study. Psychotherapy: Theory, Research, Practice, Training. 49:72-80, 2012.

Fang F. Fall K. Mittleman MA. Sparen P. Ye W. Adami HO. Valdimarsdottir U. Suicide and cardiovascular death after a cancer diagnosis. Fang F. Fall K. Mittleman MA. Sparen P. Ye W. Adami HO. Valdimarsdottir U. New England Journal of Medicine. 366:1310-8, 2012.

Fava M, Rush AJ: Current status of augmentation and combination treatments for major depressive disorder: a literature review and a proposal for a novel approach to improve practice. Psychother Psychosom 75:139–153, 2006

Fiore LD. Brophy M. Ferguson RE. D'Avolio L. Hermos JA. Lew RA. Doros G. Conrad CH. O'Neil JA Jr. Sabin TP. Kaufman J. Swartz SL. Lawler E. Liang MH. Gaziano JM. Lavori PW. A point-of-care clinical trial comparing insulin administered using a sliding scale versus a weight-based regimen. Clinical Trials. 8:183-95, 2011.

First, MB., Spitzer, RL, Gibbon M, and Williams, JBW: Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P) New York: Biometrics Research, New York State Psychiatric Institute, November 2002.

Food and Drug Administration. Center for Drug Evaluation and Research. Guidance for Industry. Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials. Draft Guidance. Revision 1. August 2012. Available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances?default.htm

Gibbons RD, Brown HC, Hur K. Is the rate of suicide among Veterans elevated? Am J Public Health 102: S1: S17-S19, 2012.

Glidden DV, Vittingho E. Modelling clustered survival data from multicentre clinical trials . Statist. Med. 23:369–388, 2004

Goodwin FK, Fireman B, Simon GE, Hunkeler EM, Lee J, Revicki D: Suicide risk in bipolar disorder during treatment with lithium and divalproex. JAMA 290:1467–1473, 2003

Goodwin FK, Jamison KR. Manic-depressive Illness. Oxford: Oxford University Press, 1990: 752.

Gottesman II, Gould TD: The endophenotype concept in psychiatry: entymology and strategic intentions. Am J Psychiatry 160:636–645, 2003

Grunebaum MF, Ramsay SR, Galfalvy HC, Ellis SP, Burke AK, et al. Correlates of suicide attempt history in bipolar disorder: a stress-diathesis perspective. Bipolar Disord. 8:551–57, 2006.

Guzzetta F, Tondo L, Centorrino F, Baldessarini RJ. Lithium treatment reduces suicide risk in recurrent major depressive disorder. J Clin Psychiatry 68: 380–3, 2007.

Gyulai L, et al. Maintenance efficacy of divalproex in the prevention of bipolar depression. Neuropsychopharmacology 28: 1374-1382, 2003.

Hanus H, Tuma I. [Prevention of suicidal activity in patients with affective disorders by treatment with lithium]. Cesk Psychiatr. 88:113-8, 1992.

Hawton K, Fagg J. Suicide and other causes of death following attempted suicide. Br J Psychiatry 152: 359-356, 1988.

Hawton K, Harriss L, Zahl D. Deaths from all causes in a long-term follow-up study of 11 583 deliberate self harm patients. Psychological Medicine 36, 397–405, 2006.

Hawton K, Zahl D, Weatherall R. Suicide following deliberate self-harm : long-term follow-up of patients who presented to a general hospital. British Journal of Psychiatry 182, 537–542, 2003.

Helbich M. Leitner M. Kapusta ND. Geospatial examination of lithium in drinking water and suicide mortality. International Journal of Health Geographics 11:19-, 2012.

Hirschfeld RM, et al. The safety and early efficacy of oral-loaded divalproex versus standard-titration divalproex, lithium, olanzapine, and placebo in the treatment of acute mania associated with bipolar disorder. Journal of clinical psychiatry 64: 841-846, 2003.

Hoge C, Ireland R, Karch D, McKeon R, Pearson J. Blue Ribbon Work Group on Suicide Prevention in the Veteran Population: Report to James B. Peake, MD, Secretary of Veterans Affairs. Washington, DC, June 30, 2008

Hollander E, Pallanti S, Allen A, Sood E, Baldini Rossi N. Does sustained-release lithium reduce impulsive gambling and affective instability versus placebo in pathological gamblers with bipolar spectrum disorders? Am. J. Psychiatry 162:137–45, 2005

Hougaard, P. Modelling Heterogeneity in Survival Data. Journal of Applied Probability 28, 695-701, 1991

Ilgen MA, Bohnert ASB, Ignacio RV, McCarthy JF, Valenstein MM,et al. Psychiatric Diagnoses and Risk of Suicide in Veterans Arch Gen Psychiatry.67:1152-1158, 2010

Isometsa E, Henriksson M, Lonnqvist J. Completed suicide and recent lithium treatment. J Affect Disord. 26:101-3, 1992.

Jeste, Dilip V. Palmer, Barton W. Appelbaum, Paul S. Golshan, Shahrokh. Glorioso, Danielle. Dunn, Laura B. Kim, Kathleen. Meeks, Thomas. Kraemer, Helena C. A new brief instrument for assessing decisional capacity for clinical research. Archives of General Psychiatry. 64:966-74, 2007

Johnson RE, McFarland BH. Lithium use and discontinuation in a health maintenance organization, American Journal of Psychiatry 153, 993-1000, 1996.

Johnson TV. Garlow SJ. Brawley OW. Master VA. Peak window of suicides occurs within the first month of diagnosis: implications for clinical oncology. Psycho-Oncology. 21:351-6, 2012

Johnston SC: Identifying confounding by indication through blinded prospective review. Am J Epidemiol 154:276– 284, 2001

Jones RM, Arlidge J, Gillham R, Reagu S, van den Bree M, Taylor PJ. Efficacy of mood stabilisers in the treatment of impulsive or repetitive aggression: systematic review and meta-analysis British Journal of Psychiatry 198, 93–98, 2011.

Kabacs, Nikolett. Memon, Anjum. Obinwa, Thom. Stochl, Jan. Perez, Jesus. Lithium in drinking water and suicide rates across the East of England. British Journal of Psychiatry. 198:406-7, 2011.

Kallner G, Lindelius R, Petterson U, Stockman O, Tham A. Mortality in 497 patients with affective disorders attending a lithium clinic or after having left it. Pharmacopsychiatry. 33:8-13, 2000.

Kang HK, Bullman TA. Risk of suicide among US veterans after returning from the Iraq or Afghanistan war zones. JAMA. 300:652-3, 2008.

Kang HK. Report to the Under Secretary. Veterans Health Administration, 2012.

Kaplan MS, Huguet N, McFarland BH, Newsom J T. Suicide among male veterans: a prospective population-based study. Journal of Epidemiology & Community Health. 61:619-24, 2007.

Kaplan MS, McFarland, Huguer N, Newsome JT. Estimating the risk of suicide among US Veterans: How should we proceed from here? Am J Public Health 102: S1: S21, 2012..

Kapusta, Nestor D. Mossaheb, Nilufar. Etzersdorfer, Elmar. Hlavin, Gerald. Thau, Kenneth. Willeit, Matthaus. Praschak-Rieder, Nicole. Sonneck, Gernot. Leithner-Dziubas, Katharina. Lithium in drinking water and suicide mortality. British Journal of Psychiatry. 198 :346-50, 2011.

Karasouli E, Owens D, Abbott RL, Hurst KM, Dennis M. All-cause mortality after non-fatal self-poisoning : a cohort study. Social Psychiatry and Psychiatric Epidemiology 46, 455–462, 2010.

Karch DL, Dahlberg LL, PhD1 Patel N, Davis TW, Logan JE, et al. Surveillance for Violent Deaths- National Violent Death Reporting System, 16 States, 2006 available at http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5801a1.htm6.

Katz I, McCarthy JF, Ignacio RV, Kemp J. Suicide among veterans in 18 States, 2005-2008: Comparisons between utilizers and non-utilizers of Veterans Health Administration (VHA) services based on data from the National Death Index, the National Violent Death Reporting System, and VHA records. Am J Pub Health. 102: S1: S105-S110, 2012

Katzman R, Brown T, Fuld P, Peck A, Schechter R, Schimmel H. Validation of a short orientation-memory-concentration test of cognitive impairment. Am J Psychiatry 140:734–9, 1983.

Kessing LV, Søndergard L, Kvist K, Andersen PK. Adherence to lithium in naturalistic settings: results from a nationwide pharmacoepidemiological study. Bipolar Disord 9:730–736, 2007.

Kessing LV, Sondergard L, Kvist K, Andersen PK. Suicide risk in patients treated with lithium. Arch Gen Psychiatry. 62:860-6, 2005.

Kovacsics CE, Gould TJ.Shock-induced aggression in mice is modified by lithium. Pharmacology, Biochemistry and Behavior 94: 380–386, 2010.

Kovacsics CE,Gottesman II, Gould TJ. Lithium's Antisuicidal Efficacy: Elucidation of Neurobiological Targets Using Endophenotype Strategies. Annu. Rev. Pharmacol. Toxicol.. 49:175–98, 2009.

Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 16:606-13, 2001.

Kunzel HE. Ackl N. Hatzinger M. Held K. Holsboer-Trachsler E. Ising M. Kaschka W. Kasper S. Konstantinidis A. Sonntag A. Uhr M. Yassouridis A. Holsboer F. Steiger A. Outcome in delusional depression comparing trimipramine monotherapy with a combination of amitriptyline and haloperidol--a double-blind multicenter trial. Journal of Psychiatric Research. 43:702-10, 2009

Lauterbach E. Felber W. Muller-Oerlinghausen B. Ahrens B. Bronisch T, et al. Adjunctive lithium treatment in the prevention of suicidal behaviour in depressive disorders: a randomised, placebo-controlled, 1-year trial. Acta Psychiatrica Scandinavica. 118:469-79, 2008.

Linehan MM. Comtois KA. Murray AM. Brown MZ. Gallop RJ. Heard HL. Korslund KE. Tutek DA. Reynolds SK. Lindenboim N. Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy by experts for suicidal behaviors and borderline personality disorder. Archives of General Psychiatry. 63:757-66, 2006

Lingam R, Scott J. Treatment non-adherence in affective disorders. Acta Psychiatr Scand 2002; 105: 164–172.

Lithium in AHFS (American Hospital Formulary Service) Drug Information. American Society of Health-System Pharmacists and Stat!Ref. Betesda, MD, 2012.

Lithium. Available at wwww.nami.org/Content/ContentGroups/Helpline1/Lithium.htm

Lithobid (Lithium carbonate, USP) Available at http://www.lithobid.net/pdfs/LIT62604_fullPI_R3.pdf

MacKinnon, D. P.; Lockwood, C. M. Hoffman, J. M., West S. G., Sheets V. A Comparison of Methods to Test Mediation and Other Intervening Variable Effects. Psychological Methods 7: 83–104, 2002

Maj M, Pirozzi R, Magliano L, Bartoli L. Long-Term Outcome of Lithium Prophylaxis in Bipolar Disorder: A 5-Year Prospective Study of 402 Patients at a Lithium Clinic. Am J Psychiatry 155:30–35, 1998.

Malone RP, Delaney MA, Luebbert JF, Cater J, Campbell M. A double-blind placebo-controlled study of lithium in hospitalized aggressive children and adolescents with conduct disorder. Arch. Gen. Psychiatry 57:649–54, 2000.

Management of Bipolar Disorder Working Group. VA/DoD clinical practice guideline for management of bipolar disorder in adults. Washington (DC): Department of Veterans Affairs, Department of Defense; 2010.

Mann JJ, Waternaux C, Haas GL, Malone KM. Toward a clinical model of suicidal behavior in psychiatric patients. Am. J. Psychiatry 156:181–89, 1999.

Mann JJ: Neurobiology of suicidal behavior. Nat Rev Neurosci 4:819–828, 2003.

Mann, J John. Arango, Victoria A. Avenevoli, Shelli. Brent, David A. Champagne, Frances A. Clayton, Paula. Currier, Dianne. Dougherty, Donald M. Haghighi, Fatemah. Hodge, Susan E. Kleinman, Joel. Lehner, Thomas. McMahon, Francis. Moscicki, Eve K. Oquendo, Maria A. Pandey, Ganshayam N. Pearson, Jane. Stanley, Barbara. Terwilliger, Joseph. Wenzel, Amy. Candidate endophenotypes for genetic studies of suicidal behavior. Biological Psychiatry. 65:556-63, 2009.

Marangell LB. Dennehy EB. Wisniewski SR. Bauer MS. Miyahara S, et al. Case-control analyses of the impact of pharmacotherapy on prospectively observed suicide attempts and completed suicides in bipolar disorder: findings from STEP-BD. Journal of Clinical Psychiatry. 69:916-22, 2008.

Marder SR. Lessons from MATRICS. Schizophrenia Bulletin 37:233-4, 2011.

Matarazzo BB, Clemans TA, Silverman MM, Brenner LA. The self-directed violence classification system and the Columbia classification algorithm for suicide assessment: A crosswalk. Suicde and Life-Threatening Behavior, 43:235-249, 2013.

McCarthy JF, Valenstein M, Kim HM, Ilgen M, . Zivin K. Blow FC. Suicide mortality among patients receiving care in the veterans health administration health system. American Journal of Epidemiology. 169:1033-8, 2009.

McGirr A, Alda M, Séguin M, Cabot S, Lesage A, Turecki G: Familial aggregation of suicide explained by cluster B traits: a three-group family study of suicide controlling for major depressive disorder. Am J Psychiatry 166:1124–1134, 2009

McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med. 285:1441-6, 1971.

McKnight RF. Adida M. Budge K. Stockton S. Goodwin GM. Geddes JR.Lithium toxicity profile: a systematic review and meta-analysis. Lancet. 379:721-8, 2012.

Meltzer HY, MD; Alphs L, Green AI, Altamura AC , Anand R, et al. Clozapine Treatment for Suicidality in Schizophrenia International Suicide Prevention Trial (InterSePT) Arch Gen Psychiatry. 60:82-91, 2003

Meyers BS, Flint AJ, Rothschild AJ, Mulsant BH, Whyte EM, Peasley-Miklus, et al. A double-blind randomized controlled trial of olanzapine plus sertraline vs. olanzapine plus placebo for psychotic depression: the study of pharmacotherapy of psychotic depression (STOP-PD). Archives of General Psychiatry 66: 838-847, 2009

Miller M, Barber C, Azrael D, Calle E, Lawler E, e t al Suicide among US veterans: A prospective study of 500,000 middle-aged and elderly men. American Journal of Epidemiology. 170:494-500, 2009.

Miller M, Azrael A, Barber C, Mukamel K, Lawler E. A call to link data to answer pressing questions about suicide risk among Veterans. Am J Public Health 102: S1: S20, 2012.

Miller M, Barber C, Young M, Azrael D, Mukamel K, Lawler E. National Death Index-linked National Health Interview Survey. Am J Public Health 102: S1: S154-S158, 2012.

Modestin J, Schwarzenbach F. Effect of psychopharmacotherapy on suicide risk in discharged psychiatric inpatients. Acta Psychiatr Scand. 85:173-5, 1992.

Muller-Oerlinghausen B, Ahrens B, Grof E, et al. The effect of long-term lithium treatment on the mortality of patients with manic-depressive and schizoaffective illness. Acta Psychiatr Scand. 86:218-22, 1992.

Muller-Oerlinghausen B, Ahrens B, Volk J, et al. Reduced mortality of manic-depressive patients in long-term lithium treatment: an international collaborative study by IGSLI. Psychiatry Res. 36:329-31, 1991.

Muller-Oerlinghausen B, Felber W, Berghofer A, Lauterbach E, Ahrens B. The impact of lithium long-term medication on suicidal behavior and mortality of bipolar patients. Arch Suicide Res 9: 307–19, 2005.

Muller-Oerlinghausen B, Muser-Causemann B, Volk J. Suicides and parasuicides in a high-risk patient group on and off lithium long-term medication. J Affect Disord. 25:261-9, 1992.

Muller-Oerlinghausen B, Wolf T, Ahrens B, et al. Mortality during initial and during later lithium treatment. A collaborative study by the International Group for the Study of Lithium-treated Patients. Acta Psychiatr Scand. 90:295-7, 1994.

Muller-Oerlinghausen B, Wolf T, Ahrens B, et al. Mortality of patients who dropped out from regular lithium prophylaxis: a collaborative study by the International Group for the Study of Lithium-treated patients (IGSLI). Acta Psychiatr Scand. 94:344-7, 1996.

Muller-Oerlinghausen B. How should findings on antisuicidal effects of lithium be integrated into practical treatment decisions?. Eur Arch Psychiatry Clin Neurosci. 253:126-31, 2003.

Muller-Oerlinghausen B. Independent effect arguments for the specificity of the antisuicidal effect of lithium. European Archives of Psychiatry & Clinical Neuroscience. 251 Suppl 2:1172-5, 2001.

National Kidney Foundation. Kidney Disease Outcome Quality Initiative (KDOQI) Chronic Kidney Disease: Evaluation, Classification, and Stratification, 2000. Available at www.kidney.org/professionals/KDOQI/guidelines_ckd/toc.htm

Nierenberg AA, Friedman ES, Bowden CL, Sylvia LG, Thase ME, Ketter T, Ostacher MJ, Leon AC, Reilly-Harrington N, Iosifescu DV, Pencina M, Severe JB, Calabrese JR, Lithium Treatment Moderate-Dose Use Study (LiTMUS) for Bipolar Disorder: A Randomized Comparative Effectiveness Trial of Optimized Personalized Treatment With and Without Lithium. Am J Psychiatry 170:102–110, 2013

Nierenberg AA, et al. Lithium treatment—moderate dose use study (LiTMUS) for bipolar disorder: rationale and design. Clinical Trials 6: 637-648, 2009.

Nierenberg AA, Fava M, Trivedi MH, et al: A comparison of lithium and T3 augmentation following two failed medication treatments for depression: a STAR*D report. Am J Psychiatry 163:1519–1530, 2006

Nierenberg AA, et al. Lithium augmentation of nortriptyline for subjects resistant to multiple antidepressants. Journal of Clinical Psychopharmacology 23: 92-95, 2003.

Nilsson A, Axelsson R. Lithium discontinuers. I. Clinical characteristics and outcome. Acta Psychiatr Scand 82:433-8, 1990.

Nilsson A. Lithium therapy and suicide risk. J Clin Psychiatry 60 Suppl 2:85-8, 1999.

Nordentopf M, Breum L, Munck LK, Nordestgaard AG, Hunding A, Laursen Bjaeldager PA. High mortality by natural and unnatural causes: a ten year follow up study of patients admitted to a poisoning treatment centre after suicide attempts. BMJ 306, 1637-1641, 1993

Ohgami H, Terao, Nobuyoshi Ishii IS, Iwata N. Lithium levels in drinking water and risk of suicide British Journal of Psychiatry 194, 464–465, 2009

Ohmura Y, Tsutsui-Kimura I, Kumamoto H, Minami M, Izumi T, Yamaguchi T, Yoshida T, Yoshioka M. Lithium, but not valproic acid or carbamazepine, suppresses impulsive-like action in rats. Psychopharmacology. Published online September, 2011.

Oquendo MA, Galfalvy H, Russo S, Ellis SP, Grunebaum MF, et al. Prospective study of clinical predictors of suicidal acts after a major depressive episode in patients with major depressive disorder or bipolar disorder. Am. J. Psychiatry 161:1433–41, 2004

Oquendo MA, Galfalvy HC, Currier C, Grunebaum MF, Sher L, Sullivan GM, Burke AK, Harkavy-Friedman J, Sublette ME, Parsey RV,Mann JJ. Treatment of Suicide Attempters With Bipolar Disorder:A Randomized Clinical Trial Comparing Lithium and Valproate in the Prevention of Suicidal Behavior. American Journal of Psychiatry. 168:10050-1056, 2011.

Ostamo A, Lonnqvist J Excess mortality of suicide attempters. Social Psychiatry and Psychiatric Epidemiology 36, 29–35, 2001

Owens D, Horrocks J, House A. Fatal and non-fatal repetition of self-harm. Systematic review. British Journal of Psychiatry 181, 193–199, 2002.

Patton, J.H., Stanford, M.S., Barratt, E.S., Factor structure of the Barratt impulsiveness scale. J. Clin. Psychol. 51, 768–774. 1995

Perroud N, Baud P, Mouthon D, Courtet P, Malafosse A. Impulsivity, aggression and suicidal behavior in unipolar and bipolar disorders. Journal of Affective Disorders 134: 112–118, 2011

Posner K, Brent D, Lucas C, Gould M, Stanley B et al. Columbia- Suicide Severity Rating Scale (C-SSRS). Available at www.cssr.columbia.edu

Posner K. Brown GK. Stanley B. Brent DA. Yershova KV. Oquendo MA. Currier GW. Melvin GA. Greenhill L. Shen S. Mann JJ. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. American Journal of Psychiatry. 168:1266-77, 2011

Preacher, K. J.; Hayes, A. F. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behaviour Research Methods 40: 879–891, 2008

Prien R, Kupfer D, Mansky P, et al: Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. Arch Gen Psychiatry 41:1096–1104, 1984

Principal Deputy Under Secretary for Health (10A), Deputy Under Secretary for Health for Operations and Management. Memorandum. Patients at High-Risk for Suicide. Washington, DC, April 24, 2008.

Report from VA Office of MH Operations to the Under Secretary for Health, 2011

Rendell, Jennifer M., et al. Developing the BALANCE trial–the role of the pilot study and start-up phase. Bipolar Disorders 6: 26-31, 2004.

Rifkin, A. Quitkin, F. Carrillo, C. Blumberg, A G. Klein, D F. Lithium carbonate in emotionally unstable character disorder. Archives of General Psychiatry. 27:519-23, 1972.

Rybin D, Doros G, Rosenheck R, Lew R. The impact of missing data on the results of a schizophrenia study. Submitted to Journal of the Society for Clinical Trials 2013.

Schou M. The effect of prophylactic lithium treatment on mortality and suicidal behavior: a review for clinicians. J Affect Disord 50:253-9, 1998.

Schrauzer GN, Shrestha KP. Lithium in drinking water and the incidences of crimes, suicides, and arrests related to drug addictions. Biol Trace Elements Res 25: 105–13, 1990.

Sheard M. Effect of lithium on human aggression. Nature 230:113–14, 1971.

Sheard MH, Marini JL, Bridges CI, Wagner E. The effect of lithium on impulsive aggressive behavior in man. Am. J. Psychiatry 133:1409–13, 1976

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 59 Suppl 20:22-33, 1998

Silverman MM, Berman AL. Sanddal ND, et al. Rebuilding the tower of Babel: a revised nomenclature for the study of suicide and suicidal behaviors. Part 1: Background, rationale, and methodology. Suicide & Life-Threatening Behavior. 37:248-63, 2007.

Sirey JA, Meyers BS, Teresi JA, Bruce ML, Ramirez M, Raue PJ. Perlick DA. Holmes D. The Cornell Service Index as a measure of health service use. Psychiatric Services. 56:1564-9, 2005.

Smith E. VHA Observational Comparative Effectiveness Study of Lithium versus Valproate for Preventing Suicide. Unpublished findings. 2012

Sobel, M. E. Asymptotic Confidence Intervals for Indirect Effects in Structural Equation Models. Sociological Methodology 13: 290–312, 1982

Spokas M. Wenzel A. Brown GK. Beck AT. Characteristics of individuals who make impulsive suicide attempts. Journal of Affective Disorders. 136:1121-5, 2012.

Swann AC, et al. Psychosis in mania: specificity of its role in severity and treatment response. Journal of Clinical Psychiatry 65: 825-829, 2004.

Swann AC, et al. Mania: differential effects of previous depressive and manic episodes onresponse to treatment. Acta Psychiatrica Scandinavica 101.6: 444-451, 2001.

Swann AC, et al. Pattern of response to divalproex, lithium, or placebo in four naturalistic subtypes of mania. Neuropsychopharmacology 26.: 530-536, 2002.

Swann AC, Dougherty DM, Pazzaglia PJ, Pham M, Steinberg JL, Moeller FG. Increased impulsivity associated with severity of suicide attempt history in patients with bipolar disorder. Am. J. Psychiatry 162:1680–87, 2005

Tein JY, MacKinnon DP. Estimating mediated effects with survival data. In: Yanai H, Rikkyo AO, Shigemasu K, Kano Y, Meulman JJ, editors. New Developments in Psychometrics: Psychometric Society Proceedings. Tokyo: Springer-Verlag; pp. 405–12, 2003

Thies-Flechtner K. Muller-Oerlinghausen B. Seibert W. Walther A. Greil W. Effect of prophylactic treatment on suicide risk in patients with major affective disorders. Data from a randomized prospective trial. Pharmacopsychiatry. 29:103-7, 1996.

Tondo L, Baldessarini RJ. Reduced suicide risk during lithium maintenance treatment. J Clin Psychiatry. 61 Suppl 9:97-104, 2000.

Tondo L, Hennen J, Baldessarini RJ. Lower suicide risk with long-term lithium treatment in major affective illness: a meta-analysis. Acta Psychiatr Scand. 104:163-72, 2001.

Tondo L, Jamison KR, Baldessarini RJ. Effect of lithium maintenance on suicidal behavior in major mood disorders. Ann N Y Acad Sci. 836:339-51, 1997.

Tondo, L. Baldessarini, R J. Hennen, J. Floris, G. Silvetti, F. Tohen, M. Lithium treatment and risk of suicidal behavior in bipolar disorder patients. Journal of Clinical Psychiatry. 59:405-14, 1998

Turecki G. Dissecting the suicide phenotype: the role of impulsive–aggressive behaviours. J Psychiatry Neurosci 30:398-408, 2005.

Turnbull B., Jennison, C. Group Sequential Methods with Applications to Clinical Trials, Chapman & Hall/ CRC Press LLC Interdisciplinary Statistics. Ch 2, pp 29-39, 2000.

Under Secretary for Health. Memorandum. Safety Plans for High Risk Veterans. Washington, DC, July 13, 2010.

US Department of Health and Human Services (HHS), Office of the Surgeon General and National Action Alliance for Suicide Prevention. 2012 National Strategy for Suicide Prevention: Goals and Objectives for Action. Washington, DC: HHS, 2012

USPSTF (US Preventive Services Task Force). Screening for Suicide Risk in Adolescents, Adults, and Older Adults: US Preventive Services Task Force Recommendation Statement. Draft. Washington, DC. 2013. Available at www.uspreventiveservicestaskforce.org/draftrec3.htm. Checked 4/30/13.

VA Office of Suicide Prevention. Suicide Prevention Coordinator Orientation Manual. Washington DC, August 2009. Updated July, 2011.

Vestergaard P, Aagaard J. Five-year mortality in lithium-treated manic-depressive patients. J Affect Disord. 21:33-8, 1991.

Watanabe KK. Kang H K. Mortality patterns among Vietnam veterans: a 24-year retrospective analysis.Journal of Occupational & Environmental Medicine. 38:272-8, 1996

Weisler RH, et al. Continuation of quetiapine versus switching to placebo or lithium for maintenance treatment of bipolar I disorder (Trial 144: a randomized controlled study). The Journal of clinical psychiatry 72: 1452, 2011.

Willson MC, et al. Valproate attenuates dextroamphetamine-induced subjective changes more than lithium. European neuropsychopharmacology 15: 633-639, 2005.

Wisniewski SR, Rush AJ, Balasubramani GK, Trivedi MH, Nierenberg AA: Self-rated global measure of the frequency, intensity, and burden of side effects. Journal of Psychiatric Practice 12:71-79, 2006

Yerevanian BI, Koek RJ, Mintz J. Bipolar pharmacotherapy and suicidal behavior. Part I: Lithium, divalproex and carbamazepine Journal of Affective Disorders 103: 5–11, 2007

Yerevanian BI, Koek RJ, Feusner JD: Pharmacotherapy and risk of suicidal behaviors among patients with bipolar disorder (letter). JAMA 291:939, 2004

Yerevanian BI, Koek RJ, Mintz J: Lithium, anticonvulsants, and suicidal behavior in bipolar disorder. J Affect Disord 73:223–228, 2003.