# APPENDICES

## Appendix A. Study Protocol

# PCORI Analysis Protocol

## Overview/Specific Aims

This will be a retrospective cohort study using VA data from Veterans who have received a diagnosis of PTSD in their medical record and are taking a first-line SRI medication for PTSD and have one of the following medications added: atypical antipsychotic (quetiapine, risperidone, or olanzapine), prazosin, mirtazapine, and tricyclic antidepressants (amitriptyline or imipramine).

**Aim 1: To compare the impact of augmenting medications on the following mental health outcomes:**

- PTSD symptoms (primary outcome- measured with the PTSD Checklist)
- Psychiatric hospitalizations and psychiatric emergency room visits
- Suicidal ideation (measured through mandatory VA screens)

**Aim 2: To compare the impact of augmenting medications on the following metabolic and cardiovascular outcomes:**

- Weight (primary outcome)
- LDL-cholesterol, HDL-cholesterol, and triglycerides
- Blood glucose and hemoglobin A1c
- Blood pressure
- Incident diagnoses of obesity, dyslipidemia, diabetes, and hypertension
- Use of medications to treat metabolic risk factors
- Cardiovascular and cerebrovascular disease events
- All-cause mortality

**Aim 3: To examine variations in the risks and benefits of augmenting medications in specific demographic subgroups:**

- Women Veterans
- Iraq and Afghanistan Veterans
- Veterans ≥ 65 years old

## Study Population

### *Inclusion Criteria*

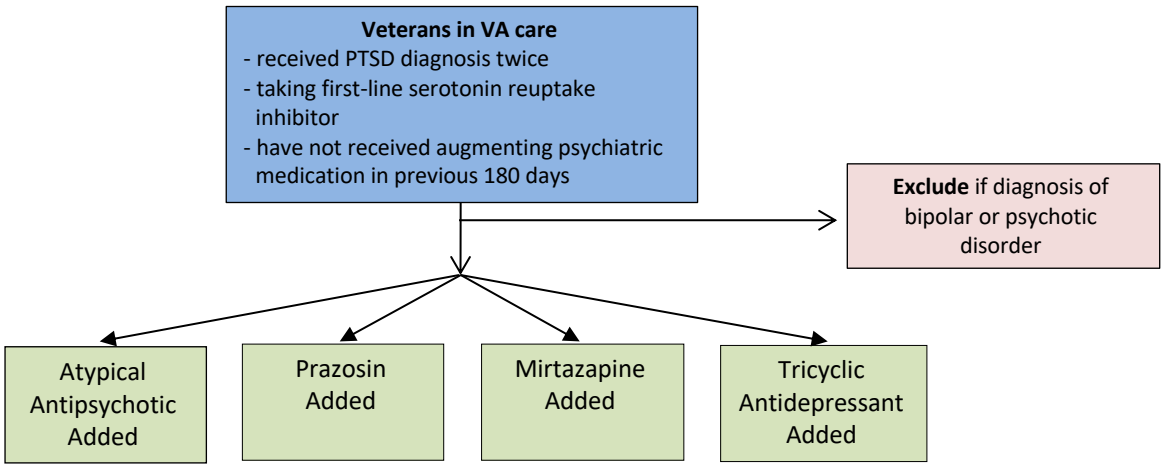
- A visit to any VA healthcare facility between 1/1/2007 and 12/31/2015
- Received a diagnosis of PTSD (ICD-9 code 309.81 or ICD 10 F43.10, .11, or .12) on ≥1 inpatient or ≥2 outpatient occasions during this timeframe
- First-line SRI antidepressant therapy for PTSD as defined in the latest VA/DoD clinical guidelines (SSRIs and venlafaxine; see Appendix 1 for medications) for at least 30 days in year prior to index date for augmenting medication.
- Has one of specified augmenting medications added (after not being on that medication for at least180-days). See Appendix 1 for medications.
- Has the augmenting medication (or one of the same class) prescribed for at least 60 days within a 120 day period
- Has at least 60 days of SRI use in year after index date

### *Exclusion Criteria*

- Diagnosis of bipolar affective disorder and/or psychotic disorder on ≥1 inpatient or ≥2 outpatient occasions and/or (see Appendix 2 for Dx codes)

This will yield 4 groups for comparison as detailed in Figure 1 below.

**Figure 1: Study Population**




## Predictor

Augmenting medication group (atypical antipsychotic, prazosin, mirtazapine, or TCA). Note groups not mutually exclusive as patients may be on multiple augmenting medications.

## Outcomes

***Aim 1: Mental Health Outcomes.***

- **PTSD symptoms**: PTSD Checklist and the Primary Care PTSD Screen
- **Psychiatric hospitalizations and emergency room visits**: Identified by primary discharge diagnosis ICD-9 codes from VA Northeast Program Evaluation Center algorithm
- **Suicidal ideation**: positive response to VA suicidality screen in Health Factors dataset

***Aim 2: Metabolic and Cardiovascular Outcomes****

| Outcome Variable | Source |
|---|---|
| Body mass index | CDW |
| Lipid levels (Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides) | CDW |
| Blood glucose | CDW |
| Hemoglobin A1c | CDW |
| Systolic and diastolic blood pressure | CDW |
| Incident diagnosis of obesity, dyslipidemia, diabetes, hypertension | CDW |
| Medications for dyslipidemia, diabetes, hypertension | CDW and Pharmacy Benefits Management Database |
| Incident diagnosis of cardiovascular disease (myocardial infarction, unstable angina, congestive heart failure, coronary revascularization) and cerebrovascular disease. | CDW |
| All-cause mortality | Vital Status File and CDW |

*For variables with multiple measurements, we will determine the average value of each variable over the one-year time period preceding and the one-year time period following the index augmenting medication prescription.

## Covariates

Covariates will be measured using the 1-year assessment period prior to the index date of initiation of the augmenting medication.

***Sociodemographics:*** age, sex, race/ethnicity, marital status, rural versus urban status.

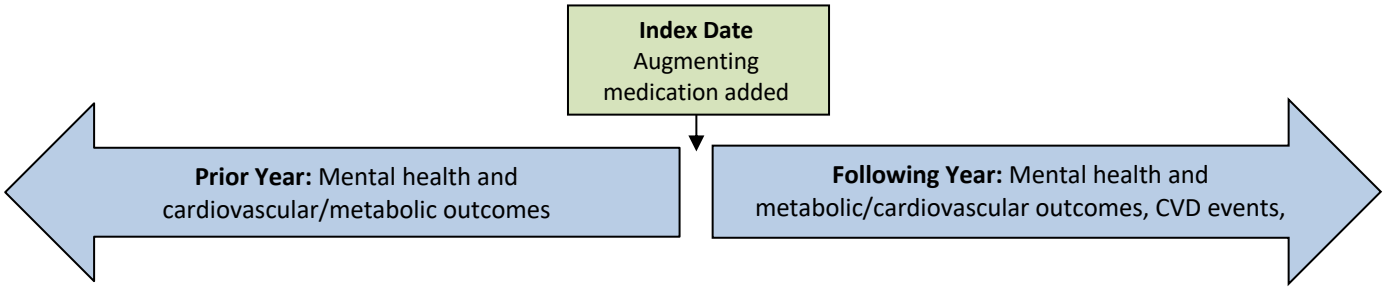
***Mental health and medical comorbidities:*** depression, anxiety disorders, personality disorders, substance abuse/dependence, alcohol abuse/dependence (ICD-9 codes from the VA NPEC). Traumatic Brain injury will be defined using the Department of Defense algorithm (800.x-804.xx; 850.x-854.xx; 905.0, 907.0)

***Service utilization factors:*** distance to nearest VA medical center, type of center (community-based outpatient clinic vs. medical center), primary care utilization, level of VA service connection, and mental health utilization (number of mental health visits).

## Analysis Plan

In our primary analyses, we will compare mental health and metabolic/cardiovascular outcomes for each of the augmentation strategies. Specifically, we will consider the initial prescription date of the augmenting medication as the "index date" and will evaluate the change in mental health and metabolic/cardiovascular parameters from one year prior to one year following the index date (Figure 2). In addition, we will compare rates of CVD events and mortality in the year following the index date and also using all available data.

**Figure 2: Overall Study Design**




***Aim 1: Mental Health Outcomes.***

**PTSD Symptom Severity.** We will use separate multivariable linear regression models to compare the change (percent and absolute) in PTSD Checklist (primary outcome) and Primary Care PTSD Screen scores from the one-year time period preceding the index date of the augmenting medication prescription to the following one-year time period. Models will be adjusted for covariates using propensity scores as outlined below. Bootstrap methods will be used to examine the robustness of inference to the standard linear regression assumptions.

**Psychiatric hospitalizations and emergency room visits.** We will construct models similar to those described above but using Poisson regression.

**Suicidal ideation.** We will construct logistic regression models similar to those described above but using presence of a positive suicidality screen as our outcome.

**Propensity Score Weighting.** This will be implemented with the Toolkit for Weighting and Analysis of Nonequivalent Groups (twang) package in R using the following steps

1. We will determine the propensity scores for each of the 4 augmenting medication groups using generalized boosted. We will include all covariates outlined above.

2. We will assess the propensity weighted balance of pretreatment covariates in the four augmenting medication groups. The twang package includes automated balance checks and will repeat iterations of the models to achieve optimal balance in addition to providing graphical and tabular balance checks for review.
3. We will evaluate overlap among the treatment groups using standard graphical and numerical diagnostics as an important assumption is that each patient will have a non-zero probability of receiving each treatment. Given our large sample size, we anticipate having adequate overlap.
4. We will estimate the weighted mean outcomes for each group using weights equal to the reciprocal of the propensity scores.
5. We will use the difference in weighted means to determine treatment effects and compare our findings with results from standard regression models using adjustment for covariates.

**Adjustment for Multiple Hypothesis Testing.** As we will be examining several outcomes, we will adjust our analyses for multiple comparisons using the Bonferroni method (i.e. defining significance at level $p < 0.05$/number of comparisons) or bootstrap based methods.

***Aim 2: Metabolic and Cardiovascular Outcomes****

**Continuous Outcomes.** We will develop separate multivariate linear regression models for each continuous metabolic outcome variable (i.e. body mass index, lipids, hemoglobin A1c) comparing values in the one year before and after the initiation of the augmenting medication. The effect of departures from the assumptions of the linear regression models will be examined with bootstrapping methods, though with the large sample sizes we anticipate little difference in the inference.

**Dichotomous Outcomes.** We will develop separate logistic regression models to compare the likelihood of receiving new diagnoses of adverse metabolic conditions (see Table 1), or initiation of new medications to treat these conditions.

**Time-to-event Outcomes.** We will construct Cox proportional hazards models to evaluate incident cardiovascular disease, stroke, and mortality in the four groups. As progression from changes in risk factors to clinical events develops over time, we will evaluate these outcomes over an extended period using all available follow-up data through 2015 in addition to the standard one-year period used for the other outcomes.

***Aim 3: Specific demographic subgroups***

We will first repeat our analyses described in Aims 1 and 2 stratified by gender then by era (OEF/OIF/OND vs. other) then by age (≥ 65 years old vs. <65). To determine heterogeneity of treatment effects in these pre-specified groups, we will test for interactions between treatment group and subgroup membership.

***Sensitivity Analyses***

**Accounting for time on and off medications.** On-treatment periods will be defined by the start date of a given prescription and the number of days of drug supplied with the fill. Percentage of follow-up time on the medication will be calculated and represented by a value from 0 to 1 and this variable will be entered into the models.

**Examination of different types and doses of medications.** We will repeat our analyses adjusting for the dose and length of time used (calculated as the total of “on” time described above) and separating into the individual antipsychotics and tricyclic antidepressants.

**Alternate outcome assessment periods.** We will repeat the CVD event and mortality analyses using longer time frames, using all available follow-up data during the study period, to determine whether the association of augmenting medication use and outcomes changes over time.

**Restricted sample.** Based on discussions with team partners, we have allowed and adjusted for use of other classes of augmenting medications during the study. To account for this change, we added a sensitivity analysis comparing results from a restricted population (patients using only one augmenting medication class during the 2-year observation period, which would more closely mimic a clinical trial) versus the inclusive real-world sample (allowing and controlling for use of other augmenting medication classes).

## Quality control

The study analyst and PI will meet at least weekly to review progress and results. Dr. Boscardin will supervise the study analyst and review propensity score methods and coding to ensure accuracy. Results will be shared with co-Investigators at regular meetings. The analyst will also be part of weekly VA Data Core meetings to address any general concerns about VA data.

## Appendix 1: VA Medication Names and Drug Class Codes

### First Line SRI PTSD Therapy

| Generic Name | VA drug class |
|---|---|
| DESVENLAFAXINE | CN609 |
| DULOXETINE | CN609 |
| VENLAFAXINE | CN609 |
| CITALOPRAM | CN609 |
| ESCITALOPRAM | CN609 |
| FLUOXETINE | CN609 |
| FLUVOXAMINE | CN609 |
| PAROXETINE | CN609 |
| SERTRALINE | CN609 |

### Atypical Antipsychotics

| | |
|---|---|
| OLANZAPINE | CN709 |
| QUETIAPINE | CN709 |
| RISPERIDONE | CN709 |

### Tricyclic Medications

| Generic Name | VA drug class |
|---|---|
| AMITRIPTYLINE | CN601 |
| IMIPRAMINE | CN601 |

### Mirtazipine

| | |
|---|---|
| MIRTAZAPINE | CN609 |

### Prazosin

| | |
|---|---|
| PRAZOSIN | CV150 |

## Appendix 2: ICD-9 Codes for Creating Cohort Dataset

| Variable | IDC9 Codes | ICD10 Codes |
|---|---|---|
| PTSD | 309.81 | F43.1x |
| Bipolar Disorder | 296.0x, 296.1x, 296.4x, 296.5x, 296.6x, 296.7, 296.8x | F30.xx, F31.xx |
| Any Psychotic Disorder | 295.xx, 298.0, 298.1, 298.4, 298.8, 298.9, 293.81, 293.82, 296.24, 296.34 | F06.0, F06.2, F20.xx, F22, F23, F24, F25.x, F28, F29, F32.3, F33.3, F53 |
| Major Depressive Disorder | 296.2x, 296.3x | F32.0, F32.1, F32.2, F32.3, F32.4, F32.5, F32.9, F33.0, F33.1, F33.2, F33.3, F33.4x, F33.9 |
| Other Depressive | 293.83, 296.9x, 298.0, 300.4, 301.11, 301.12, 301.13, 309.0, 309.1, 311 | F06.31, F06.362, F32.89, F33.8, F34.1 |
| Substance Use Disorders | 291.xx, 292.xx, 303.xx, 304.xx, 305.0x, 305.2x, 305.3x, 305.4x, 305.5x, 305.6x, 305.7x, 305.8x, 305.9x | F10.10, F10.12x, F10.14, F10.15x, F10.18x, F10.19, F10.2xx, F10.9xx, F11.10, F11.12x, F11.14, F11.15x, F11.18x, F11.19, F11.2xx, F11.9xx, F12.10, F12.12x, F12.15x, F12.18x, F12.19, F12.20, F12.21, F12.22x, F12.25x, F12.28x, F12.29, F12.90, F12.92x, F12.95x, F12.98x, F12.99, F13.10, F13.12x, F13.14, F13.15x, F13.18x, F13.19, F13.2xx, F13.9xx, F14.10, F14.12x, F14.14, F14.15x, F14.18x, F14.19, F14.2xx, F14.9xx, F15.10, F15.12x, F15.14, F15.15x, F15.18x, F15.19, F15.2xx, F15.9xx, F16.10, F16.12x, F16.14, F16.15x, F16.18x, F16.19, F16.2xx, F16.9xx, F18.10, F18.12x, F18.14, F18.15x, F18.17, F18.18x, F18.19, F18.2xx, F18.9xx, F19.10, F19.12x, F19.14, F19.15x, F19.16, F19.17, F19.18x, F19.19, F19.2xx, F19.9xx |
| Alcohol Use Disorders | 291.xx, 303.xx, 305.0x | F10.10, F10.12x, F10.14, F10.15x, F10.18x, F10.19, F10.2xx, F10.9xx |
| Personality Disorders | 301.x | F21, F60.xx, F69 |
| Anxiety | 300.02 | F41.1 |
| Insomnia | 307.41, 307.42, 307.49, 327.01, 372.02, 327.09, 780.52 | F51.0x, G47.0x |
| Obesity | 278.00, 278.01, 278.02 | E66.01, E66.3, E66.9 |
| Dislipidemia | 272.0, 272.1, 272.2, 272.3, 272.4, 272.7, 272.8, 272.9 | E75.21, E75.22, E75.249, E77.0, E77.1, E78.0x, E78.1, E78.2, E78.3, E78.4, E78.5, E78.8x, E78.9 |

| | | |
|---|---|---|
| Diabetes | 250.xx | E10.1x, E10.29, E10.31x, E10.36, E10.37Xx, E10.39, E10.40, E10.51, E10.618, E10.62x, E10.63x, E10.64x, E10.65, E10.69, E10.8, E10.9, E11.0x, E11.21, E11.29, E11.31x, E11.36, E11.39, E11.40, E11.51, E11.618, E11.62x, E11.62x, E11.64x |
| Hypertension | 401.x, 402.xx, 403.xx, 404.xx, 405.xx | I10, I11.x, I12.x, I13.xx, I15.0, I15.8, I16.9 |
| Heart Disease | 410.xx, 411.xx, 413.x | I20.1, I20.8, I20.9, I21.09, I21.1x, I21.2x, I21.3, I21.4, I24.0, I24.1, I24.8 |
| Heart Failure | 428.xx | I50.1, I50.2x, I50.3x, I50.4x, I50.9 |
| Cardiovascular Disease | 430, 431, 433.01, 433.11, 433.21,433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436 | I60.9, I61.9, I63.019, I63.119, I63.139, I63.20, I63.219, I63.22, I63.239, I63.30, I63.40, I63.50, I63.59, I67.89 |