COMPARATIVE EFFECTIVENESS PTSD TRIAL OF SEQUENCED PHARMACOTHERAPY AND PSYCHOTHERAPY IN PRIMARY CARE
(STEPS)

STUDY PROTOCOL
VERSION 5
6/27/24

Principal Investigator - John Fortney, PhD
Co-Principal Investigator – Debra Kaysen, PhD
Co-Principal Investigator – Charles Engel, MD

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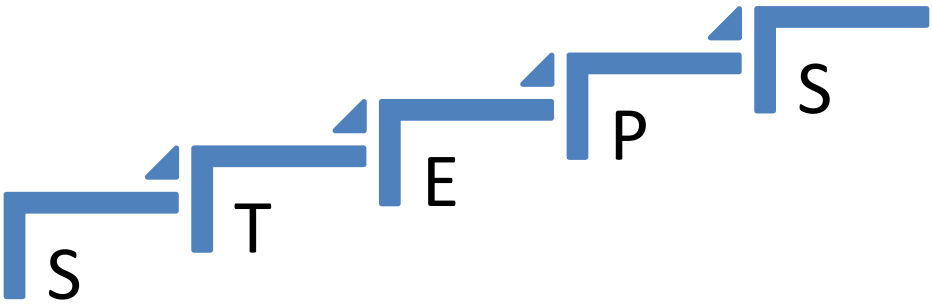


TABLE OF CONTENTS

Summary of Changes from Previous Versions:		
Affected Section(s)	**Summary of Revisions Made to Version 2**	**Rationale**
1.3, 2.5, 7, 14.2	Added two VA Medical Centers as sites.	To increase recruitment
7.2	Revised definition of specialty mental health care for exclusion criterion.	To increase recruitment
8.5	Added a data collection activity to the 4-month and 8-month chart reviews.	To collect data about receipt of trauma-focused psychotherapy in order to control for this in the data analysis.
10.2	Revised suicide ideation from a serious adverse event to *increase* in suicide ideation to an adverse event. Added suicide intention as a serious adverse event.	To comply with IRB requirements.
14.3	Added the option to view a consent video rather than read the informed consent form.	To decrease the burden of enrollment on staff.
Affected Section(s)	**Summary of Revisions Made to Version 3**	**Rationale**
1.3, 2.5, 7, 14.2	Added two Federally Qualified Health Centers as sites.	To increase recruitment
7.3	Added opt-in texts to Federally Qualified Health Centers	To increase recruitment
7, 12.2, 12.5	Reduced target sample size and recalculated power	Renegotiated contract with PCORI
1.3, 5.1, 7	Corrected errors in target sample size	Correct errors
Affected Section(s)	**Summary of Revisions Made to Version 4**	**Rationale**
8.5	Changed 90 days to 14 days for the timeframe for the pharmacotherapy adherence Changed 90 days to 4 months for the timeframe for psychotherapy adherence.	To be consistent with the timeframe of the medication survey question To be consistent with the 4-month follow-up period

1 PRÉCIS

1.1 Background and Significance

In primary care settings, PTSD frequently goes undetected and untreated. When PTSD is diagnosed in primary care, treatment is usually inadequate and outcomes are poor. This is highly problematic because many patients with PTSD prefer receiving care in primary care settings, and less than half are successfully referred to the specialty mental health setting. This is especially a concern for safety net primary settings such as Federally Qualified Health Centers and VA Medical Centers, where the prevalence of both past trauma exposure and PTSD are particularly high. However, there are effective pharmacotherapy and psychotherapy treatments for PTSD that are feasible to deliver in primary care. Due to a lack of head-to-head comparisons between pharmacotherapy and psychotherapy protocols, clinical practice guidelines for PTSD provide contradictory recommendations about pharmacotherapy and psychotherapy. In particular, PTSD clinical practice guidelines have little to offer primary care providers because so few trials have been conducted in this setting.

1.2 Study Aims

The proposed large pragmatic trial will compare, head-to-head, FDA approved antidepressant medications with a brief trauma-focused psychotherapy that is evidence-based and feasible to deliver in primary care. In addition, despite high treatment non-response rates, very few trials have examined treatment sequencing and none have done so in the primary care setting. For patients not responding to the initial treatment, the proposed research is powered to compare, head-to-head, alternative treatment sequences that are feasible to deliver in primary care. The trial will: 1) compare outcomes among patients randomized to initially receive pharmacotherapy or brief psychotherapy, 2) compare outcomes among patients randomized to treatment sequences (i.e., switching and augmenting) for patients not responding to the initial treatment and 3) examine variation in treatment outcomes among different subgroups.

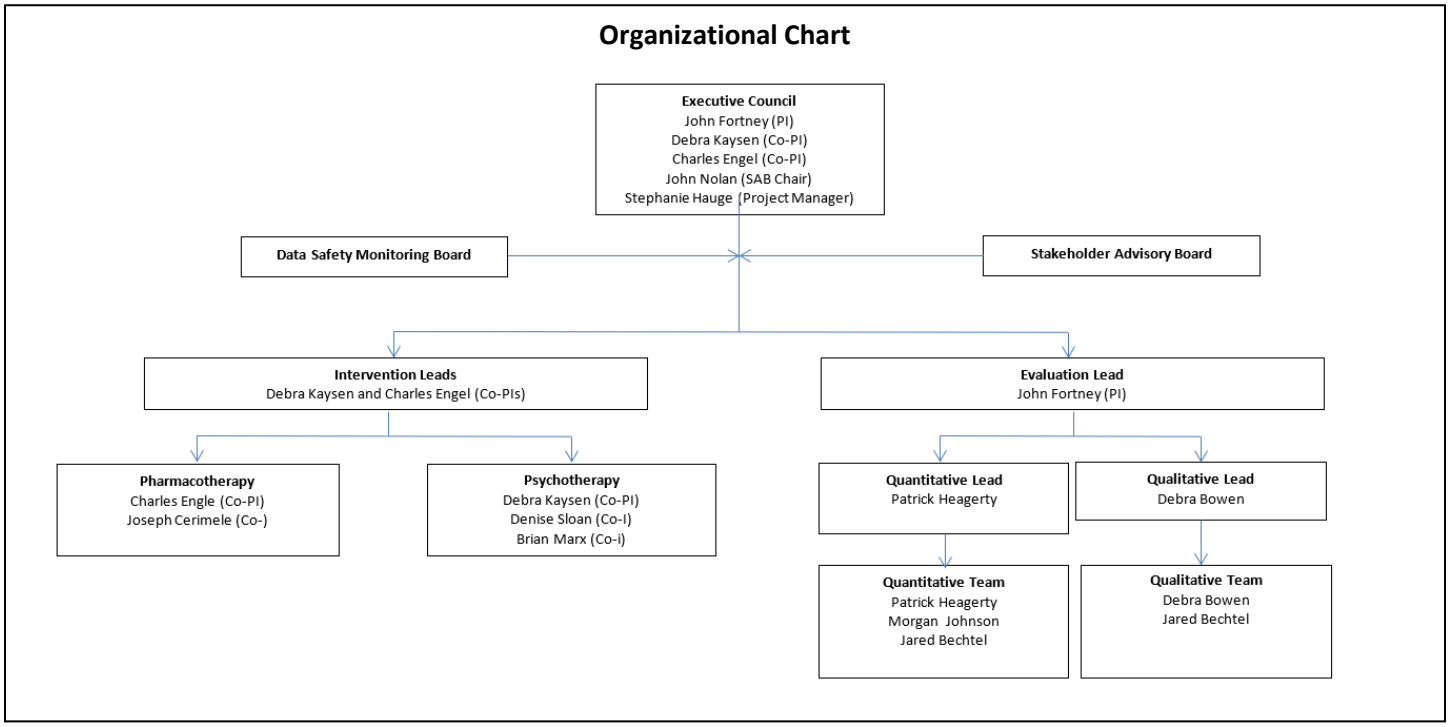
1.3 Study Description

This multi-site trial will enroll 700 patients meeting clinical criteria for PTSD from 8 Federally Qualified Health Centers and 8 VA Medical Centers. Exclusion criteria will include those needing or already receiving specialty mental health care and those who could not logistically participate in the trial. The pharmacotherapy treatments are sertraline, fluoxetine, paroxetine and venlafaxine. The psychotherapy treatment is Written Exposure Therapy. Telephone and web surveys will be used to assessed outcomes (patient treatment engagement, self-reported symptom burden, health related quality of life, and recovery outcomes) at baseline, 4- and 8-months. Patients will be the unit of the intent-to-treat analysis. Mixed-models (with multiple imputation to account

for missing data) will be used to test hypotheses.

2 STUDY TEAM

2.1 Organizational Chart



2.2 Principal Investigator

John Fortney, PhD
Professor and Director
Division of Population Health
Department of Psychiatry and Behavioral Sciences
School of Medicine, University of Washington
206.685.6955
fortneyj@uw.edu

Research Career Scientist
VA HSR&D Center of Innovation for Veteran-Centered and Value-Driven Care
VA Puget Sound Health Care System
206.764.2821
john.fortney@va.gov

Main responsibilities/Key roles: Dr. Fortney has overall responsibility for the study and is the investigator primarily in charge of the evaluation.

2.3 **Co-Principal Investigators**

Charles Engel, MD, MPH
Professor
Division of Population Health
Department of Psychiatry and Behavioral Sciences
School of Medicine
University of Washington
ccengel@uw.edu

Core Investigator
VA HSR&D Center of Innovation for Veteran-Centered and Value-Driven Care
VA Puget Sound Health Care System

Main responsibilities/Key roles: Dr. Engel has overall responsibility for the pharmacotherapy comparator.

Debra Kaysen, PhD
Professor
Division of Public Mental Health and Population Sciences
Stanford University Medical Center
dkaysen@stanford.edu
650.725.5734

Main responsibilities/Key roles: Dr. Kaysen has overall responsibility for the psychotherapy comparator.

2.4 **Co-Investigators**

Joseph Cerimele, MD
Division of Population Health
Department of Psychiatry and Behavioral Sciences
School of Medicine
University of Washington
206.221.4928
cerimele@uw.edu

Main responsibilities/Key roles: Dr. Cerimele has responsibility for the pharmacotherapy comparator and the evaluation of pharmacotherapy outcomes.

Deborah Bowen, PhD
Department of Bioethics and Humanities
University of Washington
206.616.5601
dbowen@uw.edu

Main responsibilities/Key roles: Dr. Bowen is responsible for stakeholder engagement and qualitative data collection, management and analysis.

Patrick Heagerty, PhD
Department of Biostatistics
University of Washington
206.616.2720
heagerty@u.washington.edu

Main responsibilities/Key roles: Dr. Heagerty is the lead biostatistician on the evaluation team.

Denise Sloan, PhD
Professor
Department of Psychiatry
Boston School of Medicine

Associate Director for Education
National Center for PTSD
VA Boston Healthcare System
857.364.6333
denise.sloan@va.gov

Main responsibilities/Key roles: Dr. Sloan will train therapist and evaluate therapy fidelity.

Brian Marx, PhD
Professor
Department of Psychiatry
Boston School of Medicine
bpmarx@bu.edu

Deputy Director
National Center for PTSD
VA Boston Healthcare System
857.364.6071
brian.marx@va.gov

Main responsibilities/Key roles: Dr. Marx will train therapist and evaluate therapy fidelity.

2.5 **Participating Study Sites**

Federally Qualified Health Centers

East Arkansas Family Health Center
West Memphis, Arkansas, United States, 72301
Contact: Susan Ward-Jones 870-735-3842 swjones@eafhc.org

Upper Great Lakes Family Health Center
Gwinn, Michigan, United States, 49841
Contact: Donald Similia 906-483-1325 Donald.Simila@UGLHealth.org

Family Medical Center of Michigan
Temperance, Michigan, United States, 48182
Contact: Ed Larkins 734-847-3802 elarkins@familymedical.org

Partnership Health Center, Montana
401 Railroad St. W., Missoula, MT 59802
Contact: Ellen Bluett 406-258-4442 ellen.bluett@mso.umt.edu

Health Point, Washington
955 Powell Ave SW, Renton, WA 98057
Contact: Evan Oakes 425-277-1311 eoakes@healthpointchc.org

Neighborhood Healthcare, San Diego
425 N. Date St., Escondido, CA 92025
Contact: Wendi Vierra 760-520-8340 wendi.vierra@nhcare.org

Teche Action Board, Inc.
1115 Weber Street, Franklin, LA 70538
Contact: Karla Vappie (337) 828-2550 EXT 2236 kvappie@tabhealth.org

North Central Texas Community health care center, Inc.
200 Martin Luther King, Jr. Boulevard, Wichita Falls, TX 76301
Contact: Ellaheh Ebrahim (940) 500-7065 eebrahim_md@chcwf.com

VA Medical Centers

VA Bedford Healthcare System
Bedford MA, 01730
Contact: Rosanne Schipani 781-687-2665 Rosanne.Schipani@va.gov

VA Ann Arbor Healthcare System
Ann Arbor, MI 48105

Contact: Rebeca Sripada 734-222-7432 Rebecca.Sripada@va.gov

John L. McClellan Memorial Veterans Hospital
North Little Rock, AR 72114
Contact: Jacob Painter 501-257-1740 Jacob.Painter@va.gov

Cincinnati VA Medical Center
Cincinnati, OH 45220
Contact: Nancy Nagel 513-861-3100 x5305 Nancy.Nagel@va.gov

VA San Diego Healthcare System
San Diego, CA 92161
Contact: Leslie Morland 858-552-4324 Leslie.Morland@va.gov

VA Portland Health Care System
Portland, OR 97239
Contact: Alan Teo 503-220-8262-x52461 Alan.Teo@va.gov

Ralph H. Johnson VA Medical Center
109 Bee St, Charleston, SC 29401

Acronyms	
AHRQ	Agency Healthcare Research and Quality
CHC	Community Health Center
CPT	Cognitive Processing Therapy
EHR	Electronic Health Record
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OND	Operation New Dawn
PCL	PTSD Check List
PCMHI	VA Primary Care Mental Health Integration
PE	Prolonged Exposure Therapy
PHQ-9	Patient Health Questionnaire
PTSD	Posttraumatic Stress Disorder
RCT	Randomized Controlled Trial
SAB	Stakeholder Advisory Board
SSRI	Serotonin reuptake inhibitor
SNRI	Serotonin-norepinephrine reuptake inhibitor
VA	Department of Veterans Affairs
WET	Written Exposure Therapy

Contact: Wendy A. Muzzy 843-792-8068 muzzy@musc.edu

Rocky Mountain Regional VA Medical Center
1700 North Wheeling Street Aurora, CO 80045
Contact: Bryann DeBeer 254-987-0341 Bryann.debeer@va.gov

3 ACRONYMS

4 STUDY OBJECTIVES

4.1 Primary Objective

To quantitatively compare engagement, self-reported PTSD symptom severity (primary outcome), quality of life, and recovery outcomes of primary care patients randomized to initially receive brief psychotherapy (WET) or their choice of the three SSRIs.

- Primary Hypothesis 1a – Patients randomized to receive brief psychotherapy (Arm 3) will have better outcomes than those randomized to an SSRI.

4.2 Secondary Objectives

For patients not responding to initial treatment, to quantitatively compare engagement, self-reported PTSD symptom severity (primary outcome), quality of life, and recovery outcomes of primary care patients randomized to: 1) switch from brief psychotherapy (WET) to their choice of the three SSRIs, 2) augment the SSRI with brief psychotherapy (WET), or 3) switch from one class of antidepressants (SSRI) to another class of antidepressants (SNRI - venlafaxine).

- Primary Hypotheses 2a – Non-responders randomized to an SSRI augmented by WET will have better outcomes than those randomized to switching from an SSRI to an SNRI.
- Exploratory Hypotheses 2b – Non-responders randomized to an SSRI augmented by WET will have better outcomes than those randomized to switching from WET to their choice of the three SSRIs.

Aim 3: To quantitatively examine treatment heterogeneity among subgroups of primary care patients receiving pharmacotherapy and psychotherapy.

- Primary Hypothesis 3a: Patient engagement, self-reported PTSD symptom severity, quality of life, and recovery outcomes will be poorer for: 1) veterans compared with non-veterans (controlling for combat exposure), 2) those with combat exposure compared with other types of traumas, 3) those currently prescribed benzodiazepines, 4) those taking SSRIs/SNRIs at study entry, and 5) those with self-reported substance use problems.
- Primary Hypothesis 3b: Male gender, poor access, cannabis use, and preferring pharmacotherapy will be treatment moderators that reduce the differential effectiveness of psychotherapy compared to pharmacotherapy.

Aim 4: To gain an in-depth understanding of patients' treatment experience, qualitatively examine treatment acceptability, satisfaction, and engagement, as well as the perceived benefit (or lack thereof) of treatment for patients randomized to each arm.

5 BACKGROUND AND RATIONALE

5.1 Background [CI-1][HT-1][PC-1][RQ-1][RQ-3][RQ-5]

Federally Qualified Health Centers - Federally Qualified Health Centers, more commonly known as "Community Health Centers" (CHCs), are America's healthcare safety net and are key to addressing mental health disparities across the nation. Nationwide, there are nearly 700 CHCs with over 10,000 clinic locations serving 26 million Americans [RQ-3]. Virtually all (92%) CHC patients live at or below 200% of the Federal Poverty Level, and 62% are racial/ethnic minorities. Most CHCs do not have specialty mental health programs, but rather integrate mental health treatment into primary care using the Behavioral Health Consultant model that was developed at Cherokee Health Systems (a CHC in Knoxville TN). Our Stakeholder Advisory Board (SAB) includes CHC patients, providers and administrators and we have collaborated with these stakeholders to better understand the delivery of PTSD services in CHCs and to plan this study [PC-1].

VA Medical Centers (VAMCs) – The VA healthcare system is the largest healthcare system in the country with 1,243 health care facilities, including 170 VA Medical Centers and 1,063 Community Based Outpatient Clinics serving more than 9 million Veterans per year [RQ-3]. Approximately 62% (1,218,857) of all Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND) veterans have used VA health care since 2001, and most (58.7%) have been treated for mental health disorders, including 393,139 for PTSD. Over a million Veterans (including those from previous wartime eras) receive service-connected compensation for PTSD. The VA has trained thousands of its specialty mental health providers to deliver first-line psychotherapies for PTSD (Prolonged Exposure [PE] therapy and Cognitive Processing Therapy [CPT]) in specialty mental health clinics. The VA has also integrated mental health treatment into primary care, termed Primary Care Mental Health Integration (PCMHI). PCMHI programs run two models of integrated care in parallel, the Collaborative Care Management model and the Behavioral Health Consultant model. Our SAB includes four Veterans, PCMHI leadership, and we have collaborated with these stakeholders to plan this study [PC-1].

Prevalence and Disability - PTSD can develop in individuals exposed to traumatic events such as sexual assault, serious accidental injury, natural disasters or combat. It is characterized by flashbacks, nightmares, avoidance of situations that induce trauma memories, hypervigilance, anger, and sleep deprivation. The most prevalent trauma among women with PTSD is sexual assault, and the most prevalent trauma among men with PTSD is combat. The one-year prevalence rate of PTSD is 4% in the general population, and 11.1% in primary care settings. Prevalence is even higher in publicly-funded safety-net clinics such as CHCs (20.7%) and the VA (24.5%). PTSD is a devastating disorder and a significant contributor to disability/suicidality worldwide. In primary care, 79%-88% of patients with PTSD also go on to develop clinical depression, further contributing to disability and complicating treatment. Individuals with PTSD are more likely to engage in unhealthy behaviors such as tobacco use, drug use, alcohol misuse,

and have high rates of morbidity/mortality. PTSD negatively impacts marriages, educational attainment, and occupational functioning. Providing effective treatments for PTSD in primary care settings has the potential to make an enormous impact on the quality of life for hundreds of thousands of Americans.

Usual Care – According to the National Comorbidity Study Replication, only 34.4% of individuals with current PTSD receive specialty mental health care during the course of a year. In a previous PCORI-funded large pragmatic trial (PCS-1406-19295), only 46.9% of CHC patients with PTSD offered telepsychiatrist or telepsychologist appointments actually engaged in treatment. Even within the VA's integrated system of care, only 44.6%-47.7% of veterans diagnosed with PTSD in primary care are successfully referred to specialty mental health. Among, 50,000 OEF/OIF Veterans newly diagnosed with PTSD, only 27% had ≥9 specialty mental health encounters (8-9 visits are needed for PE or CPT to be effective), and those first diagnosed in primary care were half as likely to have ≥9 encounters. The lack of engagement in specialty mental health care is highly problematic because only 13%-34% of patients receive adequate PTSD treatment in primary care (e.g., 2 months of medications or evidence-based psychotherapy) and outcomes are poor. For example, in a pragmatic trial of collaborative care for PTSD in VA primary care clinics, veterans in the usual care group showed no improvement in PTSD symptom severity (-1.3 points on the Posttraumatic Diagnostic Scale) over the course of 12 months. Likewise, in another pragmatic trial of collaborative care for PTSD in Department of Defense primary care clinics, active duty service members in the usual care group showed no improvement in PTSD symptom severity (-3.5 points on the Posttraumatic Diagnostic Scale).

Conceptual Framework [CI-1] – Lack of access and engagement in specialty mental health treatment is clearly driving poor PTSD outcomes. To close this engagement gap, more patients with PTSD need access to effective treatments in primary care settings. We conceptualize access to care as the potential ease of having encounters with healthcare providers. Integrating PTSD treatment into primary care improves geographical (i.e., travel), temporal (e.g., wait time), financial (e.g., co-pays) and cultural (e.g., stigma) access. However, even in primary care settings, poor access may be a negative treatment moderator for psychotherapy because it requires more visits than pharmacotherapy, and thus involves greater travel burden, more time commitment, and higher co-pays [HT-1]. Patients with poor access to primary care may have less frequent psychotherapy encounters than those with good access, and infrequent visits reduces the effectiveness of trauma-focused psychotherapies. Our conceptualization of patient engagement is participating sufficiently in a treatment plan to potentially experience a therapeutic effect. Treatment engagement depends on patient perceptions about access to care, and their perceived need for and expectations from treatment. With good access and adequate engagement, individuals have the opportunity to receive high quality care and improved outcomes.

Psychotherapy – Trauma-focused psychotherapies are the first-line treatment for PTSD, but are often burdensome to patients and must be delivered by highly trained therapists,

usually only available in specialty mental health treatment settings. Treatment drop-out from trauma-focused psychotherapies delivered in specialty mental health care settings is extremely high both in pragmatic trials and routine care ranging from 28.3%-47.8%. Recent meta-analyses have found that drop-out rates are higher for evidence-based trauma-focused therapies (PE and CPT) than for present centered therapy [RQ-1]. Effective and engaging therapies that are available and feasible to deliver are needed in primary care settings [RQ-5]. WET is a brief (i.e., five 40-minute sessions) trauma-focused therapy where patients write about their traumatic experience following scripted instruction. While retaining the core exposure element of other trauma-focused psychotherapies, WET does not require patient homework between sessions and requires considerably less therapist time, training and supervision. This makes WET ideal for delivery in primary care settings [RQ-5]. In contrast to the high drop-out rates for PE and CPT, drop-out rates for WET have ranged from 6.4%-14%. In a trial conducted in a civilian population, WET was significantly ($p<0.001$) more effective than waitlist control, with between group effect sizes of 3.49 and 2.18 at the 6 week and 18 week assessment, respectively. In a non-inferiority trial comparing 5 sessions of WET to 12 sessions of CPT, WET was found to be non-inferior to CPT. Drop-out rates were significantly ($p<0.001$) lower for WET (6.3%) than for CPT (39.7%). This highlights the patient-centeredness of WET compared to other trauma-focused psychotherapies [RQ-5]. WET is recommended as a first line treatment in the VA/DOD PTSD Clinical Practice Guidelines.

Pharmacotherapy – SSRIs and SNRIs are widely prescribed for patients with PTSD [RQ-5]. Two thirds (66.3%) of patients receive an SSRI or SNRI during the first year after PTSD diagnosis, with the most prescribed SSRIs being sertraline (23%), fluoxetine (11%) and paroxetine (7%) and the most common SNRI being venlafaxine (9%). According to meta-analyses, there is good evidence for the efficacy of the two FDA approved SSRIs for PTSD (paroxetine and sertraline) and the pharmacologically similar fluoxetine, as well as one SNRI (venlafaxine)[RQ-1; RQ-5]. A large meta-analysis of depression studies suggests that among these drugs, paroxetine and venlafaxine have greater side-effect profiles than sertraline and fluoxetine, and that paroxetine and venlafaxine have greater discontinuation rates than placebo or other antidepressants [RQ-1]. However, according to a recent systematic review, the frequency of adverse events associated with these medications remains poorly characterized for patients with PTSD [RQ-1]. Also, although meta-analysis suggests that the effect sizes for these medications are smaller than the effect sizes of trauma-focused psychotherapies, there are few head-to-head comparisons of pharmacotherapy and psychotherapy [RQ-1]. There are no head-to-head comparisons of pharmacotherapy and psychotherapy for PTSD conducted in the primary care setting.
8. Non-response and Treatment Sequencing - According to meta-analysis, 41% of patients with PTSD do not respond to initial pharmacotherapy [RQ-1]. For non-responders, meta-analysis suggests that augmentation with a second medication is not effective [RQ-1].72 However, there is insufficient evidence to recommend for or against switching to another medication or augmentation with psychotherapy [RQ-1]. For non-response to psychotherapy, there is also insufficient evidence to recommend for or against switching to or augmenting with pharmacotherapy [RQ-1].

Treatment Heterogeneity [HT-1] – Meta-analyses suggest that veterans are more resistant to PTSD treatment, but there are no trials with sufficient numbers of veterans and non-veterans to make head-to-head comparisons, nor to disentangle veteran status with gender and combat exposure [RQ-1]. One small head-to-head trial of pharmacotherapy versus psychotherapy demonstrated that those preferring pharmacotherapy but receiving psychotherapy had worse psychotherapy outcomes [HT-1]. The same study found that current cannabis use is associated with poorer adherence to psychotherapy but not to pharmacotherapy [HT-1]. Meta-analysis suggests that trials with more women have larger treatment effects, and this moderation effect appears to be larger for psychotherapy than pharmacotherapy [RQ-1; HT-1]. One small trial found that men and women had similar outcomes immediately after completing trauma-focused psychotherapy, but men had worse long-term outcomes [HT-1].

5.2 Study Rationale

The PCORI-AHRQ review specifically highlighted the lack of evidence about the comparative effectiveness of psychotherapy and pharmacotherapy for PTSD, and clinical practice guidelines for PTSD provide contradictory recommendations [RQ-1]. In particular, PTSD clinical practice guidelines have little to offer primary care providers because so few trials have been conducted in this setting, despite the fact that most people with PTSD do not receive specialty mental health treatment. Consequently, primary care providers are unsure about which PTSD treatments to offer their patients, and often resort to referral or prescribing benzodiazepines. The proposed pragmatic trial will determine whether the best initial choice of treatment is an SSRI or a brief trauma-focused psychotherapy that is feasible to deliver in primary care [RQ-3]. In addition, despite high treatment non-response rates, very few trials have examined treatment sequencing and none have done so in the primary care setting. For patients not responding to the initial treatment, the proposed trial is powered to compare, head-to-head, alternative treatment sequences that are feasible to deliver in primary care. Specifically, for patients failing an SSRI, the proposed trial will determine whether a different class of antidepressant (SNRI) should be recommended next or whether the SSRI should be augmented with brief trauma-focused psychotherapy [RQ-3]. Moreover, because the answers to these questions may depend on the characteristics of the patient, our large diverse sample will allow us to identify clinically meaningful treatment effect modifiers such as veteran versus civilian status, gender, concurrent drug use and patient treatment preferences. The PCORI-AHRQ review specifically highlighted the lack of evidence about whether treatment effectiveness differed by patient characteristics such as type of trauma exposure and co-occurring conditions [RQ-1].

6 STUDY DESIGN [PC-1][RQ-6]

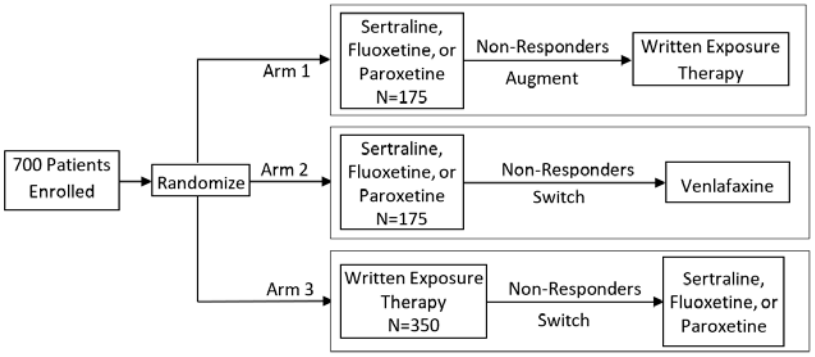
Overview: As described in Figure 1, the proposed large pragmatic trial will have three arms. Patients will initially be randomized to an SSRI (either sertraline, fluoxetine or

paroxetine based on patient preference and treatment history) or WET in a 1:1:2 allocation. The estimated 41% of patients failing to respond to the initial treatment will receive the second treatment in the sequence. Non-responders randomized to Arm 1 will have the SSRI *augmented* by WET. Non-responders randomized to Arm 2 will be *switched* from the SSRI to venlafaxine. Non-responders in Arm 3 will be *switched* from WET to an SSRI. Treatment will be delivered by primary care and integrated care staff at CHCs and VAs per recommendation for pragmatic trials [IR-5]. Encounters will be billed for by CHCs and recorded as normal workload by VAs.

Engagement Approach: As we have done successfully in our ongoing PCORI-funded pragmatic trial and for the development of this application, we have assembled a Stakeholder Advisory Board (SAB) to inform all aspects of the research from development to dissemination [PC-1]. Consumer members will include existing members of our current advisory board as well as new members selected from CHC patients enrolled in our ongoing PCORI trial (four veterans and four civilians). Policy/providers on the SAB will include existing members of our current advisory board (including two CHC Executive Directors, and a Senior Advisor at the National Association of Community Health Centers) and two new members (Director of the VA National Center for PTSD, and the Director of VA's PCMHI initiative). The consumers will meet every other month and the provider/policy members will join the meeting quarterly. We will facilitate ample opportunities for co-learning and foster a shared vision for and bidirectional commitment to the study. In addition to formal meetings, a qualitative researcher (Co-I Bowen) will reach out to consumer members individually to ensure their voice is heard. SAB members who can accept consultation will receive reasonable consulting fees. Based on consumer feedback from our first SAB meeting we made important modifications and refinements to the treatment arms. For the pharmacotherapy treatments, we now allow providers/patients to choose from a class of antidepressants (SSRIs) rather than requiring a specific antidepressant (paroxetine) as was approved in the LOI [PC-1]. This modification to the treatment comparator was approved by a Senior Program Officer at PCORI. We also made refinements to the psychotherapy protocol, allowing it to be delivered in six, 30-minute sessions (instead of five 40-minute sessions) to accommodate PCMHI session length performance metrics [PC-1]. The consumer members of the SAB also chose outcomes that were relevant to them [RQ-6] and helped revise the plans for delivering the treatment via interactive video during the COVID-19 pandemic [PC-1].

7 SELECTION AND ENROLLMENT OF PARTICIPANTS

Figure 1: Three Arm Sequenced Treatment Study Design



Study Setting and Population: This multi-site trial will enroll 700 patients meeting clinical criteria for PTSD from 8 CHCs and 8 VA sites. CHC sites were chosen because of their large size and/or successful participation in past trials. VA sites were chosen based on a data extract conducted by retired SAB member Dr. Pomerantz that identified large PCMHI programs with both psychologist and social worker therapists (needed to estimate therapist effects). Because only 11%-18% of primary care patients with PTSD are diagnosed/detected, all primary care patients will be screened for PTSD annually. Universal screening for PTSD in primary care is standard in VA. The 12 rural CHCs participating in our ongoing PCORI-funded trial successfully screened for PTSD and identified 2,802 patients with a positive PTSD screen in a 2.5 year period. Not all eligible patients were recruited to keep enrollment evenly distributed over time. We will use the new five-item PC-PTSD-5 screener which has excellent sensitivity (95%) and specificity (85%).

7.1 Inclusion Criteria [CI-2]

- Screen positive for PTSD (PC-PTSD-5 score ≥3)
- Meet PTSD diagnostic Criteria A on the Short Trauma Questionnaire
- Have high PTSD severity (PCL-5 score≥33)

7.2 Exclusion Criteria [CI-2][IR-5][PC-2]

Following Thorpe's recommendations for conducting pragmatic trials, patient exclusion criteria will be kept to an absolute minimum [PC-2; IR-5]. Patients will primarily be excluded for logistical reasons, or because they would be more appropriately treated in specialty mental health settings.

Patients will be excluded based on the following criteria:

- Patient has a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, or dementia
- Patient is currently being prescribed venlafaxine
- Patients with a new prescription for any psychotropic medication in the past 8

weeks, including dose changes

- Patient has received specialty mental health services in past 2 months, OR patient has a future appointment for specialty mental health services OR patient/provider prefers referring to specialty mental health setting. Specialty mental health is defined as seeing a mental health specialist in a non-co-located setting OR sessions are less frequent than every 2 weeks AND sessions are longer than 50 minutes in duration.
- Provider does not believe that study participation is in the best interest of the patient
- Patient is pregnant
- Patient is terminally ill
- Patient not planning to use clinic during next 8 months
- Patient is a prisoner
- Patient does not speak English or Spanish
- Patient is younger than 18 years of age
- Patient has impaired decision-making capacity and is unable to participate in the informed consent process
- Patient cannot attend in person or interactive encounters

Current use of psychotropic medications: We will allow patients to be on a stable dose of any psychotropic medication (including benzodiazepines) for 8 weeks [PC-2]. We define psychotropic medications as any antidepressant, antianxiety, antipsychotic, antimanic, sedative-hypnotic, other CNS depressant (e.g., muscle relaxers), opioid analgesic, lithium compound, or other mood stabilizers. Maintaining a stable dose will require that patients have not undergone any change in dose or frequency of administration during the period based on patient history and medical record review. Patients on a stable does of a selective serotonin reuptake inhibitor who meet the above eligibility criteria will be eligible for participation in the trial. In practice, many clinicians prescribing and patients taking medications for PTSD would consider a medication change or introducing psychotherapy if symptoms are elevated (PCL-5 $\geq$33) despite 8 weeks of stable PTSD pharmacotherapy. We believe it is important for the trial to include patients facing this common clinical scenario so as to equip clinicians and patients with data on which to inform this common treatment decision. Because we would have more power to detect treatment heterogeneity if 50% of patients were not taking SSRIs/SNRIs at baseline, we now propose to prioritize enrollment of patients not taking SSRIs/SNRIs.

7.3 Study Enrollment Procedures

To foster trust among potential study participants and facilitate patient recruitment/ retention, CHC/VA staff will recruit and consent patients. As we have done in the past, participating CHCs will obtain a Federal Wide Assurance (FWA) designating our Central IRB as having oversight of human subjects protection, allowing CHC staff to be fully engaged in research activities. VA staff research activities will be overseen by the VA's

Central IRB. The PI will train all CHC/VA staff in the recruitment and consenting processes, allowing for local flexibility in language and procedures to account for variations in community culture and clinical workflow. Once the patient is consented, CHC/VA staff will upload contact and screening information and signed consent forms to our survey group's web-interface, and the patient will be immediately randomized. Two recruitment approaches will be used: 1) handoffs during the encounter and 2) telephone outreach after the encounter. Patients screening positive for PTSD are expected to have a warm handoff to an integrated mental health provider who will administer the Short Trauma Questionnaire (from PDS-5) and the PCL-5 (both clinically appropriate following a positive PTSD screen). If the patient meets these two inclusion criteria, they will be consented by the designated staff member at the end of the encounter. Patients screening positive for PTSD who are not recruited during the encounter can also be contacted by staff afterward. Potentially eligible patients not recruited during an encounter will be identified by chart review or query of the electronic health record and contacted by staff via telephone. CHC patients with a positive PC-PTSD-5 screen or a PTSD diagnosis in the electronic health record will be sent a short opt-in text about the trial directing interested patients to call a UW researcher. The text will be sent by the CHC. The UW researcher will use the recruitment script and then assess interested patients for eligibility. Eligible patients will be consented either by CHC staff or the UW researcher. VA patients will be sent an opt-out card 10 days prior to being contacted by phone and only those not opting out will be contacted. Once the patient is consented, CHC/VA staff will indicate the patient's consent on our survey group's web-interface by uploading a PDF of the consent form, and the patient will be immediately randomized. If informed consent cannot be obtained in person, we will conduct the informed consent process over televideo or telephone. For CHC patients, e-Consent forms would be signed securely in a REDCap project hosted at UW. Clinic staff would be able to email or text a link to the e-Consent form. For VA patients, e-Consent forms will be distributed and signed using DocuSign, the VA's only approved e-Consenting platform. For patients who are unable to electronically sign the e-Consent form, we will mail written informed consent documents to be returned with postage paid return envelopes, or allow signed consent forms to be dropped off at the clinic. For faster turnaround, we may also use VA Rights Management Services (RMS) or MyHealtheVet secure transmission using encrypted email with subsequent return of wet signatures. A progress note describing study participation and randomization status will be generated for CHC/VA staff to enter into the EHR in order to notify primary care providers and therapists that the patient has been enrolled and randomized.

8 STUDY INTERVENTIONS

8.1 Psychotherapy - Written Exposure Therapy (WET)

The previously tested protocol for WET involves one 60 minutes session, followed by four 40-minute sessions (for a total of 5 sessions). The first session includes psychoeducation about symptoms of PTSD, provides a treatment rationale for approaching the trauma memory, and discusses the use of writing as a means of doing so. At the suggestion of

SAB member Dr. Pomerantz, we modified the protocol to be six sessions of 30 minutes each to account for the 30-minute session limit in the VA PCMHI setting (see WET protocol in Appendix). In sessions 2-6, patients will write about the memory of their worst traumatic event for 20 minutes, with a focus on details of the event and thoughts and feelings that occurred during the event. Patients are directed to write about the same trauma memory during each session. The therapist leaves the room while the patient writes. After returning the therapist inquires whether the patient experienced any difficulties, and addresses these with the patient. Based on feedback from our SAB, we will allow patients to audio-record their narratives if they are not comfortable writing. The therapist reads the narrative between sessions to make sure instructions were followed. Feedback about the narrative is provided to the patient at the beginning of sessions 3-6. This feedback is used to prompt the patient for writing in the current session (e.g., "You did a great job writing about the details of the event but you didn't write about the emotions you felt during the event. It is important for you to write about the emotions you felt during the event in today's writing session.") The session ends with the therapist instructing the patient to allow themselves to experience any trauma-related memories, images, thoughts, and feelings in the interval between sessions.

Interactive Video - In the VA, therapists will use VA Video Connect for televideo based encounters. If necessary, the VA research assistant can work with the local Telehealth Coordinator to send others VA-issued WiFi-enabled tablets. In CHCs, prescribers will use whichever HIPAA compliant televideo platform they have adopted (e.g. Zoom, Updox, Doxy.me, OTTO) for televideo encounters. During the session therapists will keep their video on during the entire writing time and be available if the patient has questions or needs support throughout the session. The therapist will mute their microphone while the patient is writing, so as not to distract them with ambient noise. The therapist may also ask the patient to move their camera so the therapist can observe them writing, just to ensure that they are engaged and on track and to facilitate trauma processing. It is critical that WET be delivered with fidelity in making the transition to televideo delivery. This includes three main elements that need to be preserved: measurement-based care, writing instructions and writing materials, and handling of the trauma narrative.
Measurement-based care: Measurement-based care presumes that therapists are getting updated information regarding the patient's distress (subjective units of distress, SUDS) prior to writing the exposure and after writing the exposure to inform their care and treatment plan. Changes in subjective distress are discussed with the patient as an indicator of progress, and as a measure of fear extinction. Tracking of SUDS ratings also can be used to graph symptoms and share this using screen sharing with patients or graphs can be sent to patients via secure messaging so they can see their own treatment progress. Lastly, these distress ratings are used to inform conversations regarding Written Exposure Therapy implementation during case consultation. SUDS ratings are collected verbally in session whether treatment is in-person or delivered via telehealth, thus there is no adaptation needed for telehealth delivery for this treatment element. **Materials:** Unlike most evidence-based therapies for PTSD, the number of materials necessary for Written Exposure Therapy delivery are relatively limited. Patients will need access to the

writing instructions during the session. The preferred solution is to provide this packet of session-by-session instructions for the 6 sessions in advance via regular mail or as an in-person pickup. If this is not possible the patient packets can be provided in advance via secure messaging. If that is not possible the therapist can share their screen with the instructions during the appointment or copy and paste the instructions into a chat box during the appointment to share with the patient during the session. Patients will need to have access to lined paper and a writing implement to write the trauma narrative. Typing the narrative or audio recording the narrative are not recommended strategies for completing the narrative. If there is an overriding clinical reason for typing or audio-recording the trauma narrative for a particular patient (e.g., literacy or disability) that will be tracked at the session level as a fidelity modification. Unlike in-person delivery of Written Exposure Therapy, there can be a temptation for patients to modify the narratives between sessions with televideo delivery as they retain the narrative. However, it is important to stress to patients that they should not edit or add to the narrative after the session. **Written trauma narrative:** The last challenge with adapting Written Exposure Therapy to televideo delivery is for the patient to share the written narrative with the therapist. This means that it is critical that the patient be able to get the narrative to the therapist in advance of the next session. Either having the patient read the therapist the narrative or having the patient type the narrative changes the intervention and would be seen as protocol deviations. At the same time, an essential part of treatment is for the therapist to review the narrative and provide feedback to the patient. Note that written narratives are not intended to be entered into the medical record, but rather are to be destroyed after therapy is complete. The preferred method for getting the narrative from the patient to the therapist will be for the patient to send the narrative via secure messaging. The narrative can be transferred either by scanning it with a smartphone scanning app (or printer scanner) or taking a photo of it, and then including it as an attachment to the secure message. In the VA, there is an existing patient portal system (My HealtheVet) for secure message transfer and we have secured patient training materials to instruct veterans on how to use this system. If necessary, a VA research assistant will help the veteran enroll in My HealtheVet and learn how to use the secure messaging system. For the CHCs, they will choose to either use their electronic health record's patient portal or a portal we will host at the University of Washington. This portal will be based on REDCap and patients will be able to securely upload a scanned file or photo to a location that only their therapist will be able to access. If the patient does not have the ability to scan or photograph the narrative, the patient can hold the written narrative up to the camera and the therapist can use screen capture to save the image. This option is not ideal as the image may be more difficult to read due to image degradation. The therapist must also make sure the screenshot image is de-identified and is stored in a secure location on their computer. Another option is to have the patient mail the narrative to the therapist at the clinic. This is less preferred due to both security concerns about mailing narratives, as well as concerns that the narrative may not reach the therapist in time for them to review the material prior to the next session.

8.2 **Pharmacotherapy - Antidepressants**

<u>*Step One Pharmacotherapy*</u> – Our choice of pharmacotherapy for Arms 1 and 2 was based on discussions with consumer and provider stakeholders. The consensus of stakeholders was for initial randomization to a 'choice of SSRI' comparator. Consumer stakeholders strongly preferred that their providers present them with medication options. Providers also strongly preferred options to account for patient's treatment history (i.e., failed SSRI trials due to side-effects or lack of efficacy). Individuals randomized to this SSRI comparator will receive one of three SSRIs (sertraline, paroxetine, or fluoxetine) based on patient preference and treatment history. From a scientific perspective, these three SSRIs appear to have similar effect sizes and thus, testing them as an antidepressant class is likely to yield similar treatment effects as testing them each separately. If anything, there may be a somewhat larger, but more realistic, effect as recent research suggests that giving patients with PTSD their preferred treatment improves subsequent treatment engagement (adherence, follow-up) and outcomes. In this condition, providers will assess each patient's history of SSRI treatment, including responses, and side-effects. If a patient experiences problematic side effects after taking their choice of SSRI, the provider may switch them to another of the SSRI options during the first 8 weeks of follow-up. At baseline, some primary care patients may be prescribed benzodiazepines, anticonvulsants, and/or atypical antipsychotics, though according to meta-analyses there is little evidence of their efficacy. For patients taking these medications at enrollment we will provide psychiatric consultation to the prescriber about the risks and benefits of discontinuation.

Patients on any antidepressant (including SSRIs) at enrollment who are randomized to a pharmacotherapy arm will be cross-tapered over four weeks to fluoxetine, sertraline or paroxetine (i.e., the old drug will be tapered down while the new drug is tapering up). Because patients will be randomized immediately after consenting, those randomized to a pharmacotherapy arm may have their prescription changed the same day they are consented and before the baseline survey can be completed. Therefore, for the purpose of the cross-taper, current SSRI use will be identified by the primary care provider via the EHR rather than by patient survey. Specifically, current antidepressant use will be defined as having been prescribed an antidepressant (any dose) for more than a month. Primary care providers will verify the patient has been taking the medication before implementing the cross-taper protocol. Primary care providers will be given instructions for tapering schedules for each medication. Patients will receive written instructions from their provider (developed for the trial). We will also recommend to providers a phone or clinic follow-up visit at two and four weeks to support patient adherence. We will also assess common side-effects and discontinuation symptoms (described below) via patient survey at baseline and at both the 4- and 8-month follow-up assessments. Of note, because patients will be cross-tapering SSRIs and discontinuation symptoms are typically limited to 4 weeks or less, we anticipate discontinuation symptoms will affect relatively few if any patients. Finally, these cross-tapering procedures will also be followed for those patients failing to respond to the initial treatment who are switched to another medication.

Interactive Video - Prescribers will have the option of conducting in-person (office-based) or televideo (office-based or home based) encounters with patients and occasional telephone (home-based) encounters. In the VA, prescribers will use VA Video Connect for televideo based encounters. If necessary, the VA research assistant can work with the local Telehealth Coordinator to send others VA-issued WiFi-enabled tablets. In CHCs, prescribers will use whichever HIPAA compliant televideo platform they have adopted during the COVID-19 pandemic (e.g. Zoom, Updox, Doxy.me, OTTO) for televideo encounters. Patients will use personal devices including desktops, laptops, tablets or smartphones or Medicaid-issued smartphones. A survey of the CHC teams indicated that many patients would likely use their smartphone. Three quarters (76.1%) of patients screening positive for PTSD in CHCs and recruited into a PCORI-funded trial reported owning a smart-phone, and only 15.6% reported that lack of access to a computer, tablet, or smartphone with a reliable internet connection interfered with getting the healthcare they needed. These televideo platforms allow CHC staff to send patients a link to the videoconferencing session via email or text, or for patients to enter an ID directly into a website/app. These HIPAA compliant televideo platforms also have virtual waiting rooms so that patients cannot interrupt another patient's encounter.

8.3 **Treatment Sequences:**

Based on the results of the 4-month follow-up survey (see below), we will classify patients as responders or non-responders to treatment. Specifically, we will compare the baseline and 4-month follow-up PCL-5 scores. Those not experiencing a clinically significant change (defined as <10 point change on the PCL-5) will be classified as non-responders to treatment. We conservatively expect 40% will not respond to treatment.

Arm 1: Patient failing to respond to an SSRI will be *switched* to venlafaxine. Venlafaxine was chosen as the sequenced treatment comparator for patients who are not responsive to SSRIs. Venlafaxine was chosen because 1) venlafaxine is pharmacologically different than SSRIs, with an adjunctive "selective norepinephrine" boost in addition to serotonin reuptake inhibition, and 2) venlafaxine is an evidence-based option for PTSD that relatively few primary care patients with PTSD will have been prescribed in the past. We chose not to include venlafaxine in the initial set of treatment options because: 1) discontinuation rates are somewhat higher for venlafaxine than for other antidepressant medications [RQ-1], 2) the risk of increased blood pressure (already a common problem with primary care patients) at high therapeutic dosages, and 3) primary care providers typically have less experience prescribing SNRIs than SSRIs.

Arm 2: Patient failing to respond to an SSRI will be augmented with WET.

Arm 3: Patient failing to respond to WET will be switched to an SSIR.

For patients failing to respond, the patient will be prompted to contact the clinic to discuss a treatment change and the telephone number of clinic will be provided. We will

also contact the clinic to have them schedule an appointment for the next assigned treatment. We anticipate that some patients failing treatment will not change treatment plans and that some patients responding to treatment will change treatment plans (i.e., contamination). We will record this and examine the impact of contamination bias in a sensitivity analysis.

8.4 Concomitant Interventions

8.4.1 Allowed Interventions

Patients may engage in any treatment that is available to them at any time and remain enrolled in the trial.

8.4.2 Required Interventions

None

8.4.3 Prohibited Interventions

None

8.5 Adherence Assessment [IR-2][IR-5]

Patient Adherence - Engagement/adherence will be measured using standard questions about appointment attendance and medication adherence. For pharmacotherapy, adherence will be measured as the proportion of days taking the prescribed dosage of medication in the previous 14 days (0-14 divided by 14 as an upper limit). For psychotherapy, adherence will be measured as the proportion of WET sessions attended in the previous 4 months (0-6 divided by 6 sessions as an upper limit). Thus, regardless of treatment condition, adherence will be measured on a scale from 0 to 1, allowing comparison across treatment arms.

Provider Intervention Fidelity [IR-2] – Fidelity is the degree to which the intervention is implemented as specified by the protocol. Following Thorpe's recommendations for maximizing the external validity of pragmatic trials, fidelity will be monitored, but not artificially controlled [IR-5]. For psychotherapy, CHC therapists will use a checklist for each patient encounter and upload that to a portal hosted by UW (REDCap project). For psychotherapy, VA therapists will use a checklist embedded into the progress note for each patient encounter and the information will be obtained via chart review and entered into the portal hosted by UW (REDCap project). The checklists will record the delivery of the core elements of WET (e.g., whether writing assignments were completed), the type of therapist (e.g., licensed clinical social worker, psychologist PhD) delivering WET, whether sessions were conducted face-to-face, or over interactive video or audio-only phone, and how the written narrative was made available to the therapist. For pharmacotherapy, clinic staff will review the medications list in the EHR and record which medication(s) were prescribed to the patient, and the type of prescriber (e.g., primary care physician, nurse practitioner, psychiatrist) in our survey group's web-interface. For

psychotherapy, clinic staff will review the EHR and record whether the patient received another type of trauma-focused psychotherapy (Prolonged Exposure, Cognitive Processing Therapy, or Eye Movement Desensitization and Reprocessing) and total number of encounters. As we have done successfully in the past, during the follow-up surveys we will ask patients about their adherence to the psychotropic medications they were prescribed. Likewise, we will ask patients how many WET sessions they attended.

9 STUDY PROCEDURES

9.1 Schedule of Evaluations

	Intake	Baseline	4 Month Follow-Up	8 Month Follow-up	Post Study
Clinician Assessment of Inclusion Criteria	X				
Telephone Survey		X	X	X	
Qualitative Interview					X

9.2 Description of Evaluations [CI-3][IR-6][MD-2][PC-1][PC-2][PC-3][RQ-6]

A telephone or web survey will be administered at baseline (pre-treatment), at 4-month follow-up (post initial treatment) and 8-month follow-up (post sequenced treatment for non-responders) [CI-3]. The patient telephone/web survey will be administered in English or Spanish (depending on patient preference) by the Social and Economic Sciences Center at Washington State University. All surveys will be administered by masked interviewers [IR-6] using the Computer Assisted Telephone Interviewing system. The survey group will make up to 10 phone call attempts to contact each patient, and reminder letters, emails and texts will be sent prior to the follow-up surveys [PC-2; MD-1]. All baseline interviews will be completed within 30 days of the target date. All follow-up interviews will be completed within 3 weeks before or after the target date, and follow-up rates are expected to be >80% [MD-1]. Study participants recruited from the VA will be compensated $50 for completing each of the three interviews (baseline, 4-month follow-up, 8-month follow-up) and study participants recruited from CHCs will be compensated $30, $50 and $40 for completing each interview. [PC-2; MD-1]. If patients are willing, contact information about friends and relatives will be collected at baseline, and these individuals will be consulted if the patient cannot be located for follow-up [PC-2; MD-1]. This data collection approach is consistent with Thorpe's recommendations for conducting pragmatic trials because it does not require patients to make frequent clinic visits to complete research assessments, thus minimizing patient burden and attrition bias [PC-2; IR-5]. In addition, because surveys will be completed independently of treatment, outcomes will be measured for patients dropping out of treatment [PC-2]. Prior to fielding the survey, each question will be evaluated by SAB consumer members for understandability and face validity [PC-1]. The outcome domains and instruments were selected in consultation with SAB members [PC-1][RQ-6].

9.3 Screening Evaluation

We will use the five-item PC-PTSD-5 screener which has excellent sensitivity (95%) and specificity (85%). All sites (Federally Qualified Health Centers and VA Medical Centers) routinely screen for depression at primary care visits using the 9-item PHQ-9 depression screener and the VA routinely screens for PTSD using the five-item PC-PTSD-5. The PC-PTSD-5 will be administered along with the depression screen by a nurse or physician assistant or administered by the social worker or psychologist for those patients referred to the Behavioral Health Consultant. Primary care providers typically refer patients screening positive who will administer the Short Trauma Questionnaire (from PDS-5) and the 20-item PTSD Checklist for DSM-5 (PCL-5) as part of routine care. These three instruments (PC-PTSD-5. Short Trauma Questionnaire and PCL-5) are used to determine inclusion criteria eligibility. All three instruments are short and are used routinely by Behavioral Health Consultants.

9.4 Enrollment, Baseline, and Randomization

9.4.1 Enrollment

Patients are considered to have enrolled after they have completed the informed consent AND their information (identifying information and documentation of eligibility criteria) has been entered into the research portal.

9.4.2 Baseline Assessments [IR-4]

- Demographics and insurance
- Social Support (ESSI)
- Medication Adherence (Written for STEPS)
- Side Effects (Written for STEPS)
- Health Related Quality of Life (VR-12)
- Recovery Goals (RAS) (not dominated by symptoms sub-scales)
- Criteria A Trauma Exposure (Short Trauma Questionnaire from PDS-5 at pre-baseline eligibility assessment)
- PTSD Symptoms (PCL-5 at pre-baseline eligibility assessment)
- Depression (PHQ-9)
- Sleep (PSQI-A)
- Generalized Anxiety (GAD-7)
- Alcohol Use (AUDIT-C)
- Drug Use (DAST10)
- Beliefs About Mental Health Treatment (EASI)
- Service Utilization
- Treatment History (NCS-R)
- Perceived Need (NCS-R)
- Treatment Preference (Written for STEPS)
- Access to Care (Assessment of Perceived Access to Care - APAC)

- Mobile Devices (Pew Survey)
- Health Literacy – Short Test of Functional Health Literacy in Adults (3 item screener)

9.4.3 Randomization

Randomization will be conducted at the patient level immediately before being administered the baseline research assessment. Randomization will be stratified by site so that equal numbers of patients will be allocated to the three arms at each site to avoid bias due to site-level variation in patient casemix and protocol fidelity and by SSRI/SNRI use at study entry to ensure that these more treatment resistant patients are allocated equally across the three study arms. Randomization will be blocked. We will use blocks of 4, 6, or 8, the size of which will be randomly determined to prevent local CHC/VA staff from guessing the next treatment group assignment.

9.5 Follow-Up Evaluations [IR-4][RQ-6]

- Medication Adherence (Written for STEPS)
- Side Effects (Written for STEPS)
- Antidepressant Discontinuation Symptoms (Written for STEPS)
- PTSD Symptoms (PCL-5)
- Health Related Quality of Life (SF12V)
- Recovery Goals (RAS) (not dominated by symptoms sub-scales)
- Depression (PHQ-9)
- Sleep (PSQI-A)
- Generalized Anxiety (GAD-7)
- Alcohol Use (AUDIT-C)
- Drug Use (DAST10)
- Service Utilization (Written for STEPS)
- Satisfaction (ECHO)

10 SAFETY ASSESSMENTS

10.1 Definitions of noncompliance, adverse events, serious adverse events and unanticipated problems:

- **Noncompliance:** any action or activity associated with the conduct or oversight of research involving human subjects that fails to comply with applicable regulations, the IRB's Handbook, and/or the determinations and requirements of the IRB. Noncompliance may range from minor to serious; be unintentional or willful; and may occur once, sporadically, or continuously.
    - **Protocol Violations -** an accidental or unintentional change to, or noncompliance with the IRB-approved procedures (e.g., the protocol, informed

consent document, recruitment process or study materials) without prior IRB approval. Protocol violations generally increases risk and/or decrease the benefit; affect the subject's rights, safety or welfare and/or the integrity of the research data.

- **Serious Noncompliance:** any action or omission in the conduct or oversight of research involving human subjects that affects the rights and welfare of subjects, increases risk to subjects, or compromises the scientific integrity or validity of the research.

- **Continuing Noncompliance:** a pattern of repeatedly failing to comply with applicable regulations, the IRB's Handbook, and/or the determinations and requirements of the IRB that may affect subjects' rights and welfare, increase risk to subjects, or may compromise the scientific integrity or validity of the research. Continuing noncompliance also includes frequent instances of minor noncompliance or failure to respond to a request to resolve an episode of noncompliance.

- **Adverse Event** - Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease temporally associated with the subject's participation in the research, and does not imply any judgment about causality.

- **Serious adverse event** - Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:
    - Results in death
    - Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
    - Requires inpatient hospitalization or prolongation of existing hospitalization
    - Results in a persistent or significant disability/incapacity
    - Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed above.

- **Unanticipated Problems** - Unanticipated problems involving risks to subjects are defined as any incident, experience, or outcome that meets all of the following criteria:
    - Unexpected in terms of nature, severity and risks as described in the consent form
    - Related or possibly related to participation in the research
    - Suggests that research participation places subjects at a greater risk of harm, including physical, psychological, economic, or social harm, than was previously known or recognized

10.2 **Expectedness**

There are numerous risks that are anticipated for this population of patients with PTSD and potential other comorbid mental health and substance use disorders. These risks are both study-related and non-study-related.

- Anticipated study-related risks associated with evaluation activities include:
- psychological distress due to survey questions
- potential loss of confidentiality

Study participants will be more likely to be started on or switched to FDA approved antidepressant medications or have their dosages increased than non-study participants. Likewise, study participants randomized to an arm with a Written Exposure Therapy treatment component will write about their traumatic events.
Therefore, anticipated study-related risks associated with clinical activities include:

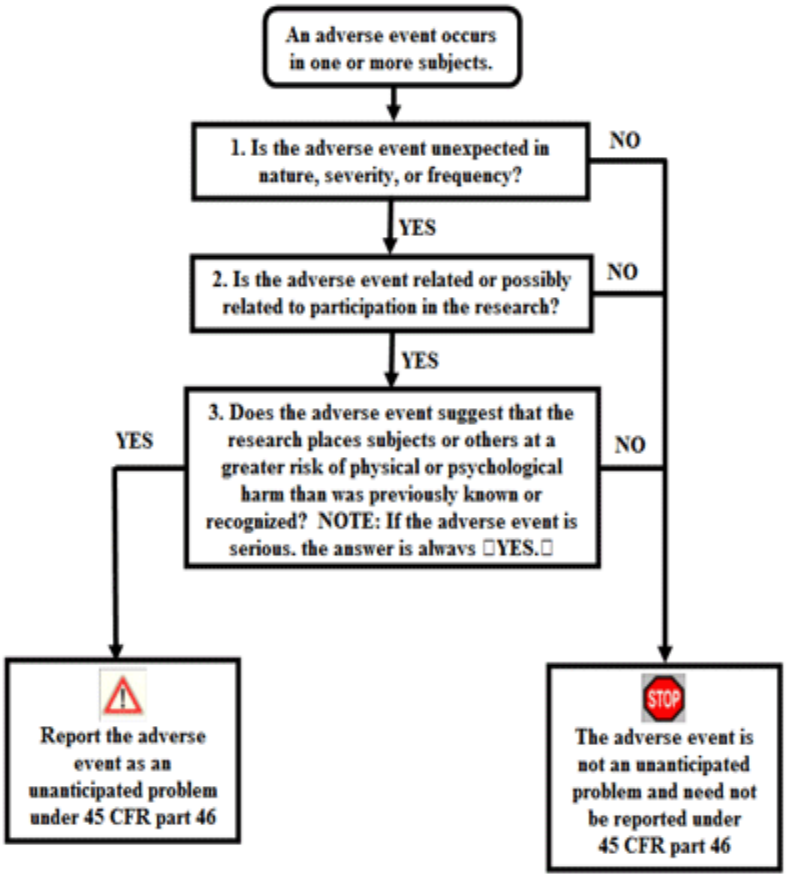
- anticipated side-effects
- psychological distress related to writing trauma narrative

Because of the severity and comorbidity of addiction and mental illness in our study population, it also anticipated that study participants will experience the following non-study related events.

- Adverse Events and Serious Adverse Events with a relatively high degree of frequency:
- Increase in suicide ideation (Adverse Event)
- Suicide intent (Serious Adverse Event)
- Suicide attempt (Serious Adverse Event)
- Death by suicide (Serious Adverse Event)
- Accidental overdose (Serious Adverse Event)
- Emergency department visits and/or hospital admissions (Serious Adverse Event)

10.3 **Determination of Unanticipated Serious Adverse Events**

Serious Adverse Events that are unanticipated must be reported to the IRB, DSMB and PCORI. To determine whether the event is an unanticipated Serious Adverse Event it must be 1) unexpected, 2) related or possibly related to the research AND 3) suggests greater risk of harm than was previously thought. The flow chart below provides an algorithm for determining whether an Adverse Event or Serious Adverse Event represents an unanticipated problem that needs to be reported under Health and Human Services regulations at 45 CFR part 46.



Step 1: Assessing whether an adverse event is *unexpected* - The vast majority of adverse events occurring in the context of research are *expected* in light of (1) the known toxicities and side effects of the treatments, 2) the expected natural progression of subjects' underlying diseases, disorders, and conditions, and 3) subjects' predisposing risk factor profiles for the adverse events. An Adverse Event is *unexpected* if the event occurs in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is not consistent with either:

- The risk of the Adverse Event is described in the informed consent document
  OR
- The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the Adverse Event and the subject's predisposing risk factor profile for the adverse event.

Step 2: Assessing whether an adverse event is *related or possibly related to participation in research* - Adverse events may be caused by one or more of the following:

- The procedures involved in the research
- An underlying disease, disorder, or condition of the subject; or

- Other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

Determinations about the relatedness of Adverse Events to participation in research commonly result in probability statements that fall along a continuum between definitely *related* to the research and definitely *unrelated* to participation in the research. *Possibly related* to participation in the research is the critical threshold for determining whether a particular Adverse Event represents an unanticipated problem. *Possibly related* is defined as "a reasonable possibility that the Adverse Event may have been caused by the procedures involved in the research.

Step 3: Assessing whether an Adverse Event *suggests that the research places subjects at a greater risk of harm than was previously known or recognized* - An Adverse Event places subjects at greater risk of harm if the event is *Serious* (a Serious Adverse Event is defined above).

10.4 Reporting Serious and Continuing Non-Compliance and Unanticipated Serious Adverse Events

Serious and Continuing Non-compliance, as well as Adverse Events that are unexpected, related or possibly related to participation in research, and *serious* warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects. Adverse events that are unexpected and related or possibly related to participation in the research, but *not* serious, may also warrant consideration of substantive changes in the research protocol or informed consent process. An unanticipated Adverse Event or Serious Adverse Event will warrant consideration of substantive changes in the research protocol or informed consent process or other corrective actions in order to protect the safety, welfare, or rights of subjects or others. Examples of corrective actions or substantive changes that might need to be considered in response to an unanticipated problem include:

- Changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects;
- Modification of inclusion or exclusion criteria to mitigate the newly identified risks;
- Implementation of additional procedures for monitoring subjects;
- Suspension of enrollment of new subjects;
- Suspension of research procedures in currently enrolled subjects;
- Modification of informed consent documents to include a description of newly recognized risks; and
- Provision of additional information about newly recognized risks to previously enrolled subjects.

10.5 Safety Monitoring

A Data and Safety Monitoring Board (DSMB) has been established for STEPS. The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and clinical effectiveness of the treatment comparators, ensuring data quality, and for monitoring the overall conduct of the study.

The DSMB is an independent group providing recommendations to the Principal Investigator (Dr. Fortney) and Co-Principal Investigators (Drs. Kaysen and Engel). The DSMB is required to provide recommendations about starting, continuing, and stopping the study. The Principal Investigator is responsible for forwarding these recommendations to PCORI. In addition, the DSMB is asked to regularly monitor the data from the study, review and assess the performance of its operations, and make recommendations, as appropriate, to Drs. Fortney, Kaysen and Engel.

11 INTERVENTION DISCONTINUATION [MD-3]

Patients may withdraw from the intervention and/or the evaluation at any time with or without their primary care provider's approval. The reason for withdrawal or termination will be recorded.

12 STATISTICAL CONSIDERATIONS

12.1 General Design Issues

The trial has three arms. Patients will initially be randomized to an SSRI or WET in a 1:1:2 allocation. Non-responders randomized to Arm 1 will have the SSRI augmented by WET. Non-responders randomized to Arm 2 will be switched from the SSRI to venlafaxine. Non-responders in Arm 3 will be switched from WET to an SSRI.

- Aim 1: To quantitatively compare engagement, self-reported PTSD symptom severity (primary outcome), quality of life, and recovery outcomes of primary care patients randomized to initially receive brief psychotherapy (WET) or their choice of the three SSRIs.
    - *Primary Hypothesis 1a – Patients randomized to receive brief psychotherapy (Arm 3) will have better outcomes than those randomized to an SSRI (Arms 1 and 2).*

- Aim 2: For patients not responding to initial treatment, to quantitatively compare engagement, self-reported PTSD symptom severity (primary outcome), quality of life, and recovery outcomes of primary care patients randomized to: 1) switch from brief psychotherapy (WET) to their choice of the three SSRIs, 2) augment the SSRI with brief psychotherapy (WET), or 3) switch from one class of antidepressants (SSRI) to another class of antidepressants (SNRI - venlafaxine).
    - *Primary Hypotheses 2a – Non-responders randomized to an SSRI augmented by WET (Arm 1) will have better outcomes than those randomized to switching from*

an SSRI to an SNRI (Arm 2).

- *Exploratory Hypotheses 2b – Non-responders randomized to an SSRI augmented by WET (Arm 1) will have better outcomes than those randomized to switching from WET to their choice of the three SSRIs (Arm 3).*

- Aim 3: To quantitatively examine treatment heterogeneity among subgroups of primary care patients receiving pharmacotherapy and psychotherapy.
  - *Primary Hypothesis 3a: Patient engagement, self-reported PTSD symptom severity, quality of life, and recovery outcomes will be poorer for: 1) veterans compared with non-veterans (controlling for combat exposure), 2) those with combat exposure compared with other types of traumas, 3) those currently prescribed benzodiazepines, 4) those taking SSRIs/SNRIs at study entry, and 5) those with self-reported substance use problems.*
  - *Primary Hypothesis 3b: Male gender, poor access, cannabis use, and preferring pharmacotherapy will be treatment moderators that reduce the differential effectiveness of psychotherapy compared to pharmacotherapy.*

12.2 **Sample Size and Randomization**

With 350 patients randomized to pharmacotherapy (Arms 1 & 2) and 350 randomized to psychotherapy (Arm 3) and assuming a 20% attrition rate and α significance level of 0.05, we will have 80% power for Hypothesis 1 to detect mean differences of 0.24 standard deviations (effect size), or 4.08 points on the PCL-5 our primary outcome. With 175 patients in each arm, and conservatively assuming a 40% treatment non-response rate, and 20% attrition rate, we will have 80% power for Hypothesis 2a to detect means differences of 0.47 standard deviations, or 7.99 points for the PCL-5 score. For the heterogeneity analyses of current versus no SSRI/SNRI use at baseline we will have 80% power to detect differences in treatment effects comparing those subjects with and without SSRIs at baseline of 0.52, 0.48and 0.47 standard deviations depending on the proportion of patients not taking SSRIs at study entry (30%, 40% or 50%). Assuming that 30% of patients are not taking SSRIs/SNRIs at study entry, we will have 80% power to detect difference in treatment effects of 8.84 on the PCL-5. Because we would have more power to detect treatment heterogeneity if 50% of patients were taking SSRIs/SNRIs at baseline, we now propose to prioritize enrollment of patients not taking SSRIs/SNRIs. If 50% of patients were taking SSRIs/SNRIs at baseline, we will have 80% power to detect differences in treatment effects of 7.99 on the PCL-5.

12.3 **Interim analyses and Stopping Rules**

No interim analyses are planned to compare intervention superiority or to stop the trial based on differences in the clinical effectiveness of the primary outcomes or safety across arms.

Potential Serious Adverse Events include suicide attempt or suicide completion and life-

threatening medication side-effects, however these are not considered to be Unanticipated Serious Adverse Events because they are not related to participation in the research. We will perform semi-annual analysis of accruing safety data. Specifically, the DSMB will discuss each serious adverse event to determine if it was study related. Because suicide attempts, suicide completions and life-threatening medication side-effects are rare events, it is not feasible to compare observed serious adverse event rates with expected rates based on published data. Specifically, there would not be sufficient power to compare observe and expected rates statistically. The DSMB will be asked to review all information associated with serious adverse events and then make a decision as to whether the study should be modified, continued or stopped.

12.4 **Outcomes**

12.4.1 **Primary outcome and endpoints:**

For Hypothesis 1a, the primary outcome is PTSD symptom severity at the 4-month follow-up as measured by the PCL-5.

For Hypothesis 2a, the primary outcome is PTSD symptom severity at the 8-month follow-up as measured by the PCL-5.

12.4.2 **Secondary outcomes**

- Side Effects (Written for STEPS) at 4- and 8-months
- Antidepressant Discontinuation Symptoms (Written for STEPS) at 4- and 8-months
- Health Related Quality of Life (SF12V) at 4- and 8-months
- Recovery Goals (RAS) (not dominated by symptoms sub-scales) at 4- and 8-months
- Depression (PHQ-9) at 4- and 8-months
- Generalized Anxiety (GAD-7) at 4- and 8-months

12.4.3 **Other Outcomes and Endpoints:**

- Sleep (PSQI-A) at 4- and 8-months
- Alcohol Use (AUDIT-C) at 4- and 8-months
- Drug Use (DAST10) at 4- and 8-months
- Treatment Engagement: Medication Adherence (Written for STEPS) and Therapy Visits (Written for STEPS) at 4- and 8-months
- Service Utilization (Written for STEPS) at 4- and 8-months
- Satisfaction (ECHO)

12.4.4 Contrasts

The primary contrast is being randomized at baseline to receive brief psychotherapy (Arm 3) versus being randomized to an SSRI (Arms 1 and 2) for the full sample.

The secondary contrast is being randomized to an SSRI augmented by WET (Arm 1) versus being randomized to switching from an SSRI to an SNRI (Arm 2) for those not responding to the initial treatment.

12.5 Data Analyses [IR-1] [HT-2][HT-3][RQ-4]

Patients will be the unit of the intent-to-treat analysis. The clustering of patients within sites may cause outcomes to be correlated across patients treated in the same site. To account for intra-class correlation and stratified randomization, healthcare system and SSRI/SNRI use at study entry will be included as fixed effects. Generalized linear models will be specified with the appropriate distribution and link functions to match the dependent variable (e.g., linear for the symptom change score, binomial for adverse events). To examine contamination bias, we will conduct a per-protocol sensitivity analysis that excludes patients who received a treatment other than the one to which they were assigned.

Hypothesis Testing [IR-1] – *Primary* Hypothesis 1 will be tested by comparing the 280 patients randomized to WET (Arm 3) completing the 4-month follow-up to the reference group specified as the 280 patients randomized to Arms 1 and 2 completing the 4-month follow-up. *Primary* Hypotheses 2a will be tested by comparing the ~56 non-responding patients randomized to Arm 1 (augmenting SSRI with WET) completing the 8-month follow-up to the ~56 non-responding patients randomized to Arm 2 (switching from SSRI to SNRI) completing the 8-month follow-up. Similarly, *Exploratory* Hypothesis 2b will be tested by comparing the ~56 non-responding patients randomized to an SSRI augmented by WET (Arm 1) to the ~56 non-responding patients randomized to switching from WET to their choice of the three SSRIs (Arm 3). To test Hypothesis 3a we will add the explanatory variables of interest (veteran/civilian status, combat vs other trauma exposure, prescribed benzodiazepines at baseline, and baseline substance use problems) to the regression testing *Primary* Hypothesis 1 (n=560 completing the 4- month follow-up) [HT-2; HT-3; RQ-4].

Exploratory Subgroup Analysis – To examine whether the results of the primary hypotheses testing are sensitive to the mode of delivery (face-to-face vs interactive video), we will dichotomously categorize study participants as mostly receiving interactive video encounters if the number of interactive video encounters is greater than or equal to the number of face-to-face encounters. This “effect modifier” will be calculated separately for the first 4-month follow-up period and the second 4-month follow-up period. The impact of this effect modifier will be assessed using the same regression specification that was used to test Primary Hypotheses 1a (Patients randomized to receive brief psychotherapy (Arm 3) will have better outcomes than

those randomized to an SSRI (Arms 1 and 2)), 2a (Non-responders randomized to an SSRI augmented by WET (Arm 1) will have better outcomes than those randomized to switching from an SSRI to an SNRI (Arm 2)), and 2b (Non-responders randomized to an SSRI augmented by WET (Arm 1) will have better outcomes than those randomized to switching from WET to their choice of the three SSRIs (Arm 3)). The effect modifier will be specified as both a main effect and as an interaction effect. A significant negative *main* effect will be interpreted as a risk factor for experiencing a smaller overall treatment effect for those patients having mostly interactive video encounters. The significance of the interaction effect will be used to determine whether mode of delivery is an effect modifier. A significant negative *interaction* term will be interpreted as interactive video as being a risk factor for experiencing a smaller psychotherapy effect and significant positive *interaction* term will be interpreted as a risk factor for experiencing a smaller pharmacotherapy effect.

12.5.1 Moderator [CI-3][HT-2][HT-3][RQ-4]

Moderator Analyses (Treatment Heterogeneity Effect) - For the treatment moderator Hypothesis 3b, we will use the method developed by the MacArthur Foundation [HT-2; RQ-4]. The treatment moderator analysis will also be conducted using the 4-month follow-up outcomes data and will compare the 280 patients randomized to WET (Arm 3) completing the 4-month follow-up to the reference group specified as the 280 patients randomized to Arms 1 and 2 completing the 4-month follow-up. The moderator variables will represent the pre-baseline time period and will not change over time [CI-3]. The moderator analysis will use the same regression specification that was used to test *Primary* Hypothesis 1. The hypothesized moderators will be added as a group as both main effects (if they were not already specified as covariates in the regressions used to test Hypothesis 1) and as interaction effects (with Arm 3). The significance of the interaction effects will be used to determine whether the patient characteristic is a treatment moderator. A negative interaction term will be interpreted as a risk factor for experiencing a smaller psychotherapy effect and positive interaction term will be interpreted as protective factor for not experiencing a smaller psychotherapy effect. The presence of significant treatment moderators will be interpreted as evidence of treatment heterogeneity, and subgroup specific treatment effects will be estimated with associated confidence intervals and displayed using a funnel plot to characterize the degree of heterogeneity. We will specify one regression equation (n=560) that simultaneously examines the following potential moderators of interest, male gender, poor access, cannabis use, and preferring pharmacotherapy over psychotherapy [HT-3]. The choice of moderators was determined by clinical judgement and prior empirical evidence (see section D.9) [HT-1].

12.5.2 Assessment of Internal and External Validity [IR-5]

To assess for internal validity, we will compare the demographic and clinical characteristics of study participants randomized to the three arms [IR-5].

To assess for external validity, we will calculate enrollment refusal rates and track reasons for refusal [IR-5].

12.5.3 Handling of Missing Data [IR-5][MD-2]

Because we are collecting comprehensive survey data, we should be observing most important baseline predictors of missingness at follow-up. We will compare the baseline characteristics of patients with and without missing outcome data [IR-5]. We will impute missing data for those with missed follow-ups to account for attrition bias rather than dropping observations with missing data [MD-2]. This approach assumes that data a missing at random (i.e., the probability of missing depends on observed data, but not unobserved data). This assumption cannot be tested.

12.5.4 Sensitivity Analyses [MD-4]

Because the missing at random assumption cannot be tested, we will conduct sensitivity analyses that consider plausible forms of non-ignorable missing outcome data, and the sensitivity of regression estimates to departures from missing at random mechanisms [MD-4]. The regression results generated by the imputed data based on the missing at random assumption and the missing not at random assumption will be compared to determine the sensitivity of our missing at random assumption.

12.6 Qualitative Data Collection, Management and Analysis

12.6.1 Qualitative Interviews [MM-1][MM-2][QM-1][QM-2][QM-4][RQ-6]

Because the patient's treatment experience is a critical outcome that the survey instruments may not adequately capture, we also propose to conduct semi-structured qualitative interviews with patients [RQ-6; QM-1]]. Sample: Qualitative interviews will be conducted with a purposively selected sample of patients (n≈60) [QM-2]. Patients will be recruited at the end of their 8-month follow-up interview [QM-1; MM-1]. The aim is to achieve maximum variation in the patient sample so that we have the broadest understanding of patient experiences. Initially, patients will be sampled to achieve variation in treatment arms and level of engagement [QM-2; QM-4; MM-2]. As we conduct interviews, we will analyze the data in order to refine the interview guide and begin to identify preliminary themes or findings. As qualitative findings become available, we may make minor revisions to the interview guides and consider new directions with regard to sampling [QM-2]. This iterative process (moving between sampling, data collection and analysis) will allow us to use early findings to target recruitment and monitor for saturation (the point at which no new findings are emerging from the interviews).

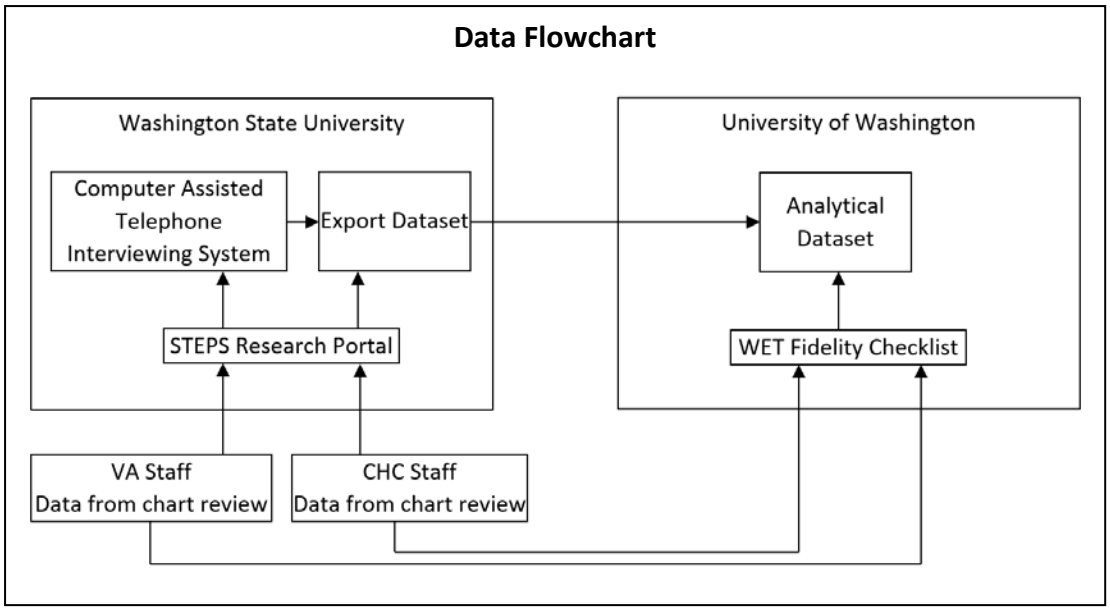
12.6.2 Qualitative Data collection [MM-1]

All interviews will be conducted by phone. Patients will be audio-consented by the qualitative investigator or a trained research assistant just prior to the interview. Interviews will be conducted using interview guides that will be developed during the course of the study in partnership with our SAB. The purpose of the interviews will be to gain an in-depth understanding of why treatments were found to be more or less effective and for which types of patients [MM-1]. Therefore, we will initially focus our patient interviews on the fit between the patient and the treatment, treatment preferences, access, engagement and perceived helpfulness of treatment. However, we will also pursue other issues that emerge naturally during the interviews and incorporate them into our interview guides. Thus, the inductive qualitative data collection, coding, analysis, and interpretation will be integrated activities, thus ensuring that the interpretation of findings is well grounded in the data. Qualitative findings will help us interpret why patients randomized to Arm 1, Arm 2 or Arm 3 had better outcomes [MM-1].

12.6.3 Qualitative Data Management and Analysis [MM-3][QM-1][QM-3][QM-4]

Audio recordings of the interviews will be transcribed and entered verbatim, along with any observation field notes, into a qualitative data analysis and management software package (Atlas.ti) that enables researchers to mark blocks of text with thematic codes, explore relationships among codes, and between codes and participant groups [QM-1]. Our qualitative expert and a trained research assistant will analyze the transcripts and notes [QM-3]. We will follow the 5-phase analysis strategy described by Crabtree and Miller (describing, organizing, connecting, corroborating/legitimizing, representing) [QM-1]. To accomplish the describing and organization steps we use an immersion-crystallization approach in which the team reads and discusses the data (immersion) to identify key findings (crystallization) [QM-3]. We will develop an initial set of inductively derived categories that tag or mark critical segment of data. These analytical categories will likely reflect the broad range of characteristics noted above, as well as others that emerge through the data analysis process. After consensus is reaching on these tagging conventions, what we often refer to as codes, a codebook will be established. To ensure consistency in data analysis, the team will meet regularly to discuss the discrepancies and emerging findings. After all of the data has been reviewed once, the team will begin a comparative analysis, where categories of tagged text (codes) are analyzed to identify cross-cutting patterns. For the connecting phase, we will compare our findings to the survey results [MM-3]. For the corroborating/ legitimizing phase, we will present our findings to the SAB to confirm/disconfirm or refute insights [QM-4]. For the representing phase, we will meet with the SAB to discuss the best ways of sharing understandings and interpretations that are meaningful to our target audience.

13 DATA COLLECTION AND QUALITY ASSURANCE [IR-3]



13.1 **Quality Assurance**

For the telephone survey, the case disposition for each study participant will be tracked in the research portal maintained by Washington State University. Contact information will be checked for completeness by project assigned clinic site coordinators and by UW project managers. For each study participant, their contact history will be documented and recorded. Washington State University employs an interviewer dialing protocol using a computer assisted telephone interview CATI system that will provide for up to ten for every telephone number in telephone survey samples. Contacts by telephone are tracked in the CATI's sample administration disposition system.

Supervised Interviewing - Interviewer performance is monitored to provide feedback and ensure adherence to standardized survey interview scripts. Interviewers are scored and assessed for quality interviewing and standardized performance. Interview performance reports are produced through the CATI system. Survey monitors and survey supervisors monitor 5% to 10% of interviews and score performance and evaluate interviewers throughout the course of the project. Monitors are able to listen to the interviews on the telephone and to observe the data being entered by the interviewer as the interview is being conducted. The monitoring process focuses on the interviewer's use of probing and feedback phrases, accuracy in reading questions and recording responses, rapport with respondent, and ability to persuade respondents to complete the interview. Immediate feedback is given to each interviewer who is monitored, on his/her performance during the interview. Supervisors use reports to work with individual interviewers to improve

cooperation rates, productivity rates, and overall performance of interviewers on the surveys.

CATI Controls - The CATI system provide computer screen display for viewing each question and coded response options. Prior to the start of interviewing the CATI programmed questionnaire is tested in multiple ways to ensure question branching matches the ended pathway as designated in the final WORD version of the questionnaire. The branching is tested by the programmer, the study director, the survey supervisors, survey interviewers, and survey sponsor for accuracy. Pretesting with mock interviews helps test the interview flows as intended aurally. Scenario testing and question by question testing is conducted to make sure all response option coding instructs desired question branching. The CATI system controls the progress and routing through the survey interview. At each question response options are coded and only possible response options are allowed for entry by the interviewer. This controls for entry error by interviewers. Error is also reduced by thorough training on the questionnaire with an experienced survey supervisor prior to interviewing. All interviewers on monitored, performance scored, and provided with feedback on performance during calling and specifically on the project surveys. In the event that survey questions are missed inadvertently respondents are recalled to verify or recollect the data.

Questionnaire Data Quality Review - The data are extracted from pretest interviews and for interviews to ensure that data is generated for every variable in the survey. A frequency listing showing each question and its response options, the number of responses and percentages of responses are printed and reviewed by SESRC and UW project directors for accuracy. Each question is also reviewed for the occurrence of missing data. Since the survey and all questions are voluntary, a small number of missing responses are not uncommon. Early review of the survey responses allows for early intervention if a larger than expected frequency of missing or nonresponsive data are discovered. The survey will also be reviewed for outliers on numeric variables and strategies can be implemented to help counter missing or outlier data if it is found to occur. As much as possible strategies will be implemented to prevent missing responses. Examples of these strategies include allowing for “don’t know”, and “refused” responses so that interviewers can progress with the interviews. With the coding of “don’t know” responses, strategies such as an alternative question with prespecified categorical response can be used to help respondent that expresses they can’t be precise and the interviewer encourages best estimates. Other options include providing open ended follow-up questions to explore why a respondent cannot provide an answer.

13.1.1 Site Monitoring

For each site, we will run biweekly report that provides aggregate counts of the following data points:

- # Patients meeting inclusion criteria
    - # Patients meeting exclusion criteria

        - # Patient has a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, or dementia
        - # Patient is currently being prescribed venlafaxine
        - # Patients with a new prescription for any psychotropic medication in the past 8 weeks, including dose changes
        - # Patient has received specialty mental health services in past 2 months, OR patient has a future appointment for specialty mental health services OR patient/provider prefers referring to specialty mental health setting. Specialty mental health is defined as seeing a mental health specialist in a non-co-located setting OR sessions are less frequent than every 2 weeks OR sessions are longer than 30 minutes in duration.
        - # Provider does not believe that study participation is in the best interest of the patient
        - # Patient is pregnant
        - # Patient is terminally ill
        - # Patient not planning to use clinic during next 8 months
        - # Patient is a prisoner
        - # Patient does not speak English or Spanish
        - # Patient is younger than 18 years of age
        - # Patient has impaired decision-making capacity and is unable to participate in the informed consent process
        - # Patient cannot attend in person or interactive encounters
        - # Patients not assessed for eligibility
    - # Eligible patients not enrolled
        - # Unable to contact
        - # Refused
            - Reason for refusal
    - # Eligible patient consented

These site reports will be used to monitor the various steps in the recruitment process. For sites recruiting fewer patients than expected, these reports will be used to identify problems in the recruitment process (e.g., not screening patients for PTSD, not attempting to recruit patients, patients refusing to participate).

13.1.2 Methods to prevent and monitor missing data [MD-1]

Retention in the evaluation will be monitored and controlled. The goal for retention in the evaluation (i.e., completion of the 4- and 8-month follow-up telephone surveys) will be >80%. Standard interviewing times will include early evenings and weekends. The dialing protocol requires 10 valid call attempts: two morning attempts, two afternoon attempts, and six evening attempts at different hours of the evening. Reminder letters, texts and emails about follow-up interviews will be sent out to patients a month in advance and patients will be called two weeks prior to their scheduled interview to determine whether the interview needs to be rescheduled. We will also include a $5 bill

in the reminder letter. Another reminder letter will be mailed after 5 phone attempts. Study participants will be compensated financially for completing each of the three interviews (baseline, 4-month follow-up, 8-month follow-up). The survey will be administered in either English or Spanish depending on the preference of the study participant. We will monitor survey progress through reports posted on-line. These reports will show the number of completed interviews and the number of interviewer hours for the project on a daily basis as well as cumulative totals and project goals. To monitor interviewer performance, we use the reports produced by our CATI system providing individual and overall totals for interviewing by interviewer and by project, for any time period selected. Data Collection uses these reports to work with individual interviewers to help improve the cooperation rate, productivity rate and overall performance of that individual on a project. There will be a regular established communication between SESRC and UW to make notification for study participants that have inaccurate or no longer working telephone numbers. SESRC will monitor the survey progress through reports (i.e. case level disposition reports and productivity reports). SESRC will communicate survey progress and outcomes through on-line and/or periodic reporting. These reports will show the number of completed interviews for each survey wave. When study participants are lost to follow-up, SESRC will document the reason why the follow-up was not completed (e.g., refused, unable to contact, etc.).

Retention in treatment (for the two treatment comparators TCC and TER) will be monitored but not controlled. Qualitative interviews will be conducted with patients who did and did not engage in treatment in order to identify the reasons why some patients did not initiate or dropped out of care.

14 PARTICIPANT RIGHTS AND CONFIDENTIALITY

14.1 Institutional Review Board (IRB) Review

There are 2 IRBs providing oversight for the STEPS Trial.

- **University of Washington IRB**
  - Review of adverse events
  - Evaluation Activities
    - Telephone/web survey
    - Qualitative interviews
    - Data analysis
  - Federal Wide Assurance for CHCs
    - Eligibility assessment
    - Chart review
    - Informed consent
    - Clinical activities

Four universities are ceding oversight of research activities to the University of

Washington IRB:

- Washington State University
- University of Michigan IRB
- Oregon Health & Science University
- Stanford University

- **VA Central IRB**
    - Clinical activities at VA Medical Centers
    - Review of adverse events
    - Eligibility assessment
    - Chart review
    - Clinical activities

In addition to the VA Central IRB, the local Research & Development offices will provide regulatory oversight for each VA Medical Center site.

14.2 Data Use Agreements

Each of the eight VA Medical Center sites and the University of Washington (on behalf of all sub-contractors) will sign a Data Use Agreement. This Agreement establishes the terms and conditions under which the VA Medical Center will provide and the University of Washington will use data for the STEPS trial.

14.3 Informed Consent Forms

Community Health Center (CHC) staff will obtain informed consent for three reasons. First, the local CHC staff are in the best position to explain the study to the patient using language that is familiar to them. Second, local CHC staff are in the best position to understand the patients' medical care context and to answer questions about how the study could impact that care. Third, patients have trust in the local CHC staff and feel comfortable asking questions or expressing concerns. To avoid coercion the patient's primary care provider will not be involved in obtaining informed consent. Following a positive PTSD screen, CHC staff will talk with the patient and their provider to assess study eligibility prior to engaging the patient in the informed consent process. CHC staff will approach patients screening positive for PTSD after the screening has taken place. The informed consent process may take place the same day the patient visited the clinic. If there is not an opportunity to engage the patient in the informed consent process on the same day as their visit, CHC staff will telephone the patient and schedule a time for them to come back to the clinic to undergo informed consent.

The consent form will be available in English and in Spanish. The CHC staff member trained to obtain informed consent will find a private location to conduct the informed consent process. The staff member will explain the informed consent process and then give the patient time to read the consent form. The staff member will offer to read the consent form to the patient. CHC patients will also have the option of viewing a video

instead of reading the consent form. After the patient has read the consent form, the staff member will give the patient the opportunity to ask questions and then assess the patient's understanding of the purpose of the study, the procedures and the risks and benefits. Once the consent form has been signed, the staff member will make two copies and give one to the patient. The other will be stored in a locked cabinet locally. A pdf of the scanned signed consent form will be uploaded to the research portal at Washington State University. If informed consent cannot be obtained in person, we will conduct the informed consent process over televideo or telephone. E-Consent forms would be signed securely in a REDCap project hosted at the University of Washington (UW).

A progress note describing study participation and randomization status will be generated for CHC staff to enter into the EHR in order to notify the PCP that the patient has been enrolled and randomized.

14.4 **Participant Confidentiality**

Washington State University

In developing survey procedures, Washington State University follows the code of professional ethics and practices of the American Association for Public Opinion Research. That code states that "Unless the respondent waives confidentiality for specified uses, we shall hold as privileged and confidential all information that might identify a respondent with his or her responses. We shall also not disclose or use the names of respondents for non-research purposes unless the respondents grant us permission to do so." To that end, all interviewers and employees at Washington State University are trained regarding professional ethics and confidentiality and in understanding their role as a professional researcher with regard to keeping interviews confidential and to act in ways that will not introduce bias or compromise research objectives.

Furthermore, to ensure that survey respondents cannot be identified from their survey responses Washington State University will follow federal guidelines for protection of human subjects, and will adopt the following procedures:

- Will maintain two separate files in separate locations. One file will contain the survey administration files, which include subject identifiers such as phone number and individual names. The second file will contain the survey responses. These two files will be linkable with a study ID.
- Will keep all computer records on password protected computers in locked offices and all paper files in locked file cabinets in locked offices. No data collected from respondents will be stored on laptops or portable devices.
- Will encrypt all files sent via email or on external devices to the Sponsor's study coordinators.

Data Protection – Washington State University has facilities that ensure data protection

and disaster recovery practices. All the data files have primary storage on SESRC's data collection servers residing within Washington State University's Departmental Server Facility. One server is a file server that is used to store information and documents for current and archived projects. A second server is used to host the organization website, collect and store data from surveys, as well as to serve as a web and database server. A third server is used as a printer server. All three servers are used as DNS servers (Domain Name Server). We also have three dedicated web servers for management of file backup and survey data collection. Backup servers are connected to each of the main network servers at each location, and are available if either of the main local area networks fails. A RAID array of hard drives is used for backup of daily interviewing data and is currently set for RAID. Thus, survey data is written simultaneously to multiple servers and drives to ensure backup of each interview as it is being conducted. Interview data is stored on both the main and backup servers as it is collected. Additionally, a daily backup is created at the end of each day's calling at 11 p.m. every evening, and is stored on the server hard drives. Once a month, all of the daily files are backed-up again on a compact disk (CD) and archived for later retrieval if necessary. The facility has restricted access to authorized personnel only, with 24-hour video surveillance and registered electronic key access. The facility also is equipped with humidity and temperature controls, exclusive air conditioning, a Halon fire detection and suppression system and Uninterrupted Power Source (UPS). Servers sit behind Washington State University's firewall system at all times and all machines are protected with the latest Symantec Antivirus software. In case of system failure, all servers are running on a RAID array, mirroring working drives. In addition, nightly backups of all data are created and archived using a synthetic-fulls procedure on a 90-day and 14-day rotation. In addition to Washington State University's Departments Server Facility monitoring, the survey unit maintains its own remote server monitoring software designed to give notice to our network administrators in the case of attempted intrusion, system overloads or system failure.

University of Washington

All study staff will be trained by the Principal Investigator on the protection of participants' rights, especially in areas relevant to confidentiality. All staff will acknowledge in writing that they will abide by the University's and current study's rules and procedures pertaining to the rights of participants, confidentiality, and data safety in general. They will acknowledge that any lapse could result in disciplinary action or termination. In addition, the proposed project will adhere to the following general rules of data safety: 1) all staff will sign a written commitment to maintain an atmosphere of confidentiality, which will include not discussing confidential study information with anyone outside the study team and not attempting to learn the identity of an individual participant; 2) all questionnaire data will be marked only by a non-identifying ID number; 3) all identifying information (consent forms, contact information for follow-up interviews) will be kept separate from data gathered from participants and kept double-locked, either in locked cabinets in locked rooms or in password-protected files in password-protected computers or systems; 4) all questionnaire data gathered from

participants will be kept double locked; 5) non-study personnel will at no time be permitted to view identifying information; 6) all electronic data containing identifiers will be maintained with password protection. The following data sources will contain patient identifiers: consent forms, and participant locator forms. Consent forms will have the signature of the participant. Locator forms will contain the participant's name, study ID, medical record #, current address and phone number, as well as the addresses and telephone numbers of contacts. For survey data, each study participant will be given a unique, but non-identifying number. No names or other identifying information will appear in the survey data. Electronic copies of the interview data will be stored on a secured (password protected) server and files are backed up each night by UW IT.

14.5 Study Discontinuation

The STEPS trial can be discontinued by the University of Washington IRB or the VA Central IRB.

15 ETHICAL CONSIDERATIONS

The 1979 The Belmont Report and 1991 Publication of the Common Rule guide the ethical principles being followed by the STEPS trial.

The 1996 Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule guides the protocols for sharing patient health information between organizations.

16 COMMITTEES

- Executive Council
- Stakeholder Advisory Board
- Data and Safety Monitoring Board

17 PUBLIC USE DATASET [IR-7]

The Patient Centered Outcomes Research Institute requires that all funded studies generate a public use de-identified dataset and data dictionary. This Open Science Data Repository has not yet been created, but the Inter-university Consortium for Political and Social Research (ICPSR) at the University of Michigan has been funded to create such a repository. The public use de-identified dataset and data dictionary for STEPS will be furnished to this repository in the format required.

18 PUBLICATION OF RESEARCH FINDINGS [PC-4]

Publication of the results of this trial will be governed by the Executive Council and written publication guidelines for the STEPS investigators.