DEPRESSION TRIALS NETWORK
SUICIDE ASSESSMENT METHODOLOGY STUDY
(SAMS)
PROTOCOL

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PURPOSE AND OBJECTIVES

The primary objective of this pilot study is to develop research methodology and evaluate assessment tools which can be applied in 'real world' clinical practice settings, and to adequately describe and measure the occurrence and natural course of treatment emergent suicidality after initiation of Selective Serotonin Reuptake Inhibitor (SSRI) pharmacotherapy.

To fulfill this goal, we propose the following **specific aims**:

SPECIFIC AIM 1
Develop Methodological Techniques and Evaluate Measurement Tools to Assess Associated Effects of Initiation and Dosage Increase of SSRI Therapy: To evaluate which of the following domains associated with suicidality are impacted during initiation and dose increase during SSRI therapy: anxiety, agitation, panic, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, manic states, hopelessness, and the subjective intensity of the desire to self-harm. We expect a positive relationship between all these domains with frequency and intensity of suicidal ideation.

SPECIFIC AIM 2
Assess the Feasibility of Current Approaches to Monitoring SSRI Therapy in Real-World Clinical Settings: To determine the frequency of monitoring required, as well as the domains and markers within each domain that are most important when monitoring for the progression of suicidal states during SSRI pharmacotherapy in real-world settings. We expect there to be a limited number of distinct patterns associated with the progression of suicidal ideation during SSRI treatment.

SPECIFIC AIM 3
Assess Suicidal Ideation Associated with Initiation and Dosage Increase of SSRI Therapy: To determine the frequency and intensity of new onset or increase in pre-existing suicidal ideation in a cohort of patients when: a) commencing SSRI therapy, and b) when increasing dose during SSRI therapy.

BRIEF OVERVIEW OF THE DEPRESSION TRIALS NETWORK FOR THIS STUDY

This pilot study will utilize the infrastructure of the National Institute of Mental Health's (NIMH) Depression Trials Network (DTN). This infrastructure was developed for and successfully used in Sequenced Treatment Alternatives to Relieve Depression (STAR*D) and is designed to maximize scientific integrity, patient safety and the effective and cost-efficient performance of the project.

The study will be overseen by the DTN's National Coordinating Center (NCC) (The University of Texas Southwestern Medical Center) and Data Coordinating Center (DCC) (Epidemiological Data Center at the University of Pittsburgh). Patients will be seen at primary care or specialty care sites at the following DTN Regional Centers: The University of Texas Southwestern Medical Center, University of California at San Diego, Virginia Commonwealth University, Massachusetts General Hospital, Columbia University, Laureate Psychiatric Clinic and Hospital - Tulsa, University of North Carolina at Chapel Hill, Vanderbilt University, University of California at Los Angeles Neuropsychiatric Institute, Los Angeles Biomedical Research Institute at Harbor - UCLA Medical Center, University of Michigan, Tuscaloosa Veterans Affairs Medical Center, Northwestern University, Clinical Research Institute – Kansas, and University of Pittsburgh Medical Center.

All Regional Centers and the DCC have their own Institutional Review Boards, which will be asked to approve this protocol and supervise their local DTN affiliate.

OVERVIEW

The context of current research into suicidal states is one of mounting societal and regulatory pressures to understand the etiology of suicidal behavior and predict its occurrence in the face: a) of limited empirical evidence to guide clinicians in the identification and treatment of suicidality and b) of increasing apprehension among the general public about some antidepressant treatments. In light of major unanswered questions about the emergence of suicidal processes in major depressive episodes (MDEs), conceptualization of the unique contribution to risk represented by SSRI therapies is made all the more difficult. It is clear that diverse research approaches will be needed to adequately study the broad, difficult questions related to the etiology of suicidal behavior emerging during antidepressant therapies, to predict its occurrence, and to advise clinical management. It is equally clear that a fuller understanding of this relationship is hampered by problems with suicide-related nomenclature, measurement, and a lack of understanding about the nature, course and intensity of the prototypic suicidal process found in depressed states. Therefore, we propose a pilot study to answer a number of basic, preliminary questions about duration of monitoring and procedures to be used during initiation and dose increase of pharmacotherapy with a common SSRI agent. We also seek to clarify the course of suicidal ideation during treatment with an SSRI using a protocol designed to facilitate ongoing measurement of common domains found in suicidal states utilizing standardized ratings and techniques suitable for use in real-world clinical settings.

BACKGROUND

In the United States, approximately 30,000 Americans died annually of suicide-related causes during 2001 and 2002,[1] while an additional 350,000-450,000 were treated in medical settings for nonfatal intentional self harm,[1-3] and nine million others struggled with suicidal ideation.[4] Suicidal states can occur in the absence of diagnosable psychopathology, but one of the single most salient risk factors for both suicidal behavior and ideation is the presence of depression.[5, 6] An estimated 50-80% of all persons who commit fatal or nonfatal suicidal acts have been diagnosed with affective illness,[7] and upwards of 50-60% of all patients experiencing suicidal ideation have either a diagnosable depressive disorder or severe, subjective dysphoria.[8, 9] In the context of recurrent major depressive disorder (MDD), a history of suicidal behavior is associated with earlier onset of affective illness,[10] more episodes,[11] greater risk of relapse,[12] and greater lifetime functional impairment.[13, 14] Even with this increased severity of illness, however, suicidal tendencies experienced by patients during (MDEs) have been shown to respond to antidepressant treatment, with no statistical differences in remission rates after treatment for those who experience suicidal ideation during the episode.[15, 16]

Despite their reported success in the treatment of suicidal states, there is growing concern that antidepressant treatment may in fact have a paradoxical effect on a minority of those so treated, actually inducing suicidal states in susceptible individuals.[17-20] Early case reports described an antidepressant-induced state characterized by akathisia-like restlessness, suicidal ideation and strong, self-destructive impulses.[21-23] While evidence from randomized controlled trials of selective serotonin reuptake inhibitors (SSRIs) compared to placebo in children and adolescents suggests an increased risk of SSRI-associated suicidal behavior,[24, 25] to date, investigations of the suicide-related risk to adults undergoing SSRI treatment have produced contradictory findings.[26-38] However, in October, 2004, available evidence led to the US Food and Drug Administration (FDA) to introduce a preliminary product labeling change concerning the use of antidepressants in adults.[39] This FDA advisory suggests that, during the "initial few months" of a course of antidepressant therapy or at times of dose changes, "patients should be observed for worsening suicidality and unusual changes in behavior," including anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania and mania." The warning was issued prior to the completion of FDA-sponsored meta analyses of adult clinical trial information, and the lack of specific language it contains reflects

the limited empirical evidence available. As such, major, unanswered questions remain regarding the emergence, course, and outcome of suicidal states occurring during SSRI pharmacotherapy.

Specifically, little actual research exists to inform the duration and frequency of monitoring for suicidality in clinical settings during SSRI treatment initiation or dose change, and no standardized ways of assessing the intensity and associated dangerousness of suicidal states have been forthcoming. A lack of information about the nature and course of suicidal states as they exist in real-world settings during SSRI-related treatment of MDEs leaves practicing clinicians without information and procedures critical to patient management during SSRI pharmacotherapy.

We believe that in order to be usable in real world clinical practice, any standardized clinical procedure designed to monitor suicide-related phenomena should be able to detect changes at the level of the individual patient over time; therefore changes in the frequency and intensity of suicidal states should be evident even within relatively small samples. As such, we propose conducting a pilot study looking at the association between starting a selective serotonin reuptake inhibitor and the occurrence and progression of suicidal ideation over the first 8 weeks of treatment in a sample of 300 patients, using a research-informed regimen for monitoring and assessing suicidal ideation and impulses. As aggressive, standardized treatment is necessary to ensure adequate care of depressed, suicidal patients,[40] study physicians will be asked to provide measurement-based care following a rigorous treatment protocol using commonly used SSRI antidepressants. The protocol used in this study is based on that used in the recently-completed, National Institute of Mental Health (NIMH) - funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial.[41-43] During the study we propose to carry out regular evaluations of the intensity of suicidal ideation, specifically monitoring those domains associated in the FDA warning with SSRI-induced activation - i.e., anxiety, agitation, panic, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, and manic states--as well as evaluating the level of depressive symptomatology and quality of life. The goal of this pilot study is to develop and evaluate a methodology and measurement tools to describe and adequately measure the occurrence and natural course of suicidal ideation after initiation of SSRI pharmacotherapy in representative settings and to evaluate the presence and timing of suicidal ideation and associated symptoms.

As early as 1991, complaints about fluoxetine-induced suicidal states were being addressed by the FDA through public meetings where patients and relatives testified to adverse experiences while undergoing pharmacotherapy for the treatment of depression.[17] In one of the earliest published case reports, Teicher and colleagues (1990) described their clinical experience with six, widely different patients who developed intense suicidal ideation a mean of 26 days after initiation of SSRI treatment.[47] These clinicians described the suicidal state, even among the formerly suicidal, as "more intense, obsessive, and violent than anything the patients had previously experienced." After tapering affected patients off of SSRI therapy, Rothschild and Locke (1991) attempted to restart fluoxetine in three patients who had previously made a serious suicide attempt during treatment with the drug.[48] All three developed what they termed "severe akathisia" during re-initiated SSRI treatment, a state confirmed in several subsequent reviews and multiple additional case reports.[49-53] The onset of this akathisia-like state appeared to occur anywhere from half a day to a few months following SSRI initiation or dose increase, and did not abate until sometime after discontinuation of the treatment.[49] In many cases, it appeared to be associated with pressured thoughts, stereotypic movements, irritability, and a strong desire to self-harm. Despite the number of case reports that appeared over the next few years, attempts to characterize these cases statistically found "no consistent relationship" between suicidal behavior and: a) dose of SSRI agent, b) the time of onset after starting the medication, or c) response during dose increase.[54] Therefore, in 1993, a task force of the American College of Neuropsychopharmacology concluded that "there was no scientific evidence indicating that SSRIs could trigger suicidal behavior."[55]

The concerns have not disappeared. In 2004, the British Committee on Safety in Medicine (CSM) expert working group made public its latest review on the safety of SSRIs,[25] based on clinical trial data from pharmaceutical companies. The CSM noted that the assessment of a causal association between SSRIs and suicidal behavior is difficult because (1) suicide is a rare event, even in patients with depressive illness and (2) suicidal behavior is a symptom of the underlying disease. The report goes on to say, from available clinical trial

data, both published and unpublished, that a "modest increase" in the risk of suicidal thoughts and self-harm for SSRIs compared to placebo cannot be ruled out, although neither can a modest benefit. To date, there is insufficient evidence from clinical trial data to conclude that there is any marked difference between members of the class of SSRIs, or between SSRIs and other antidepressants, with respect to their influence on suicidal behavior. However, mounting public concern and some findings from this meta analyses ultimately led the CSM to issue warnings on the use of SSRIs among children and adolescents.[25]

In June, 2005, the US FDA extended its version of the warning used in SSRI product labeling to include adults.[30] The warning is prefaced by statements indicating that the FDA is currently conducting "a complete review of all available data to determine whether there is an increased risk of suicidality (suicidal thinking or behavior) in adults being treated with antidepressant medications," which was not finished at the time of issuance of the warning. It goes on to state that "[Meanwhile,] adults being treated with antidepressant medications, particularly those being treated for depression, should be watched closely for worsening of depression and for increased suicidal thinking or behavior. Close watching may be especially important early in treatment, or when the dose is changed, either increased or decreased."[30]

Given the FDA warning, amplification of the available evidence base guiding the clinical management of suicide risk in depressed states is especially pertinent. Specifically, the length of time over which increased vigilance is required, frequency of assessment, the suicide domains to be monitored, and assessment procedures to be used are all unspecified. In an attempt to contribute to the body of work addressing these practical clinical issues, we propose conducting a pilot study which would closely monitor a cohort of moderately-to-severely depressed patients after initiation of protocol-driven treatment with an SSRI antidepressant over the course of the first eight weeks of treatment. A standardized assessment procedure and approach developed for this purpose would be utilized in order to monitor the consistency and progression of suicidal states existing at baseline or emerging during care.

CONCISE PROJECT SUMMARY

The primary objective of this study is to develop new methodological techniques to evaluate treatment emergent suicidal ideation, specifically during the initiation of SSRI antidepressant treatment, and during times of dosage escalation. The goals of the study are: 1) to develop an assessment battery to quantify and qualify the severity of suicidal ideations, 2) to determine the appropriate frequency and duration of assessments required to adequately evaluate treatment emergent suicidal ideation, 3) to evaluate the presence of associated symptoms (i.e. anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania and mania) and 4) to identify the most critical time periods during which suicidal ideation appears or worsens (i.e. how long after initiation of treatment or dosage increase).

In all, 300 adult subjects with MDD, between the ages of 18 and 75, may be enrolled at primary and specialty care sites across the USA. All subjects will be treated with an SSRI for 8 weeks. The choice of SSRI used in treatment will be at the discretion of the study physician at each site. For this study, physicians will choose from the following six SSRIs: citalopram, escitalopram, sertraline, paroxetine, paroxetine-CR, and fluoxetine.

Subjects may learn of the possibility of participating from their treating physician or clinic staff or may be recruited via flyers and/or posters. Informed consent will be signed before assessment of the subjects is undertaken for the study. After informed consent is obtained, study staff will perform a diagnostic interview and determine eligibility for participation (see inclusion and exclusion criteria). The diagnosis of MDD (non-psychotic) will be made by the study investigators and be based on the Psychiatric Diagnostic Screening Questionnaire (PDSQ) and a DSM-IV MDD checklist (MDDC). After the initial screen and baseline evaluation, patients will be seen in the clinic for evaluation bi-weekly (weeks 2, 4, 6, and 8) for assessment of medication tolerability, and symptom severity including suicidal ideation and associated symptoms. The baseline visit will take up to 2 hours and each follow up visit up to 1 hour.

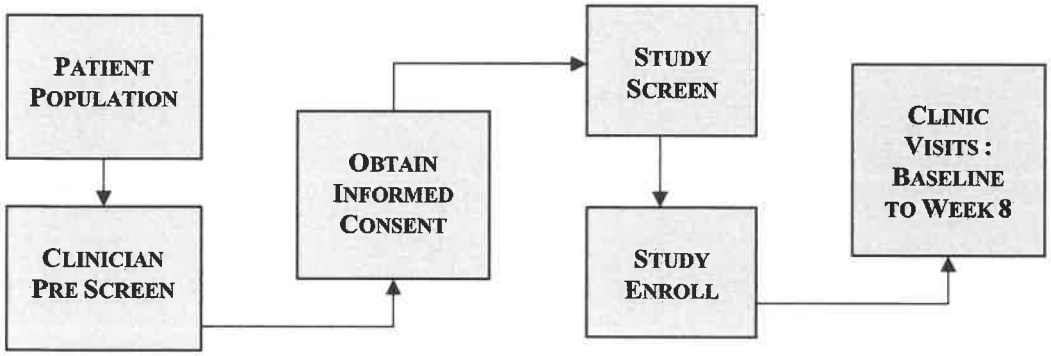
Study physicians will use the General Principles for Treatment Implementation (see Appendix I) and symptom severity and tolerability information to make dose adjustments as recommended by the critical decision point Dosing Tables (see Appendix II). Clinical management will be informed by the Quick Inventory of Depressive Symptomatology Clinician rated version (QIDS-C_{16}) (Rush et al. 2003, Trivedi et al. 2004) which evaluates depression symptom severity, the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) (Wisniewski et al. 2005), and the Systematic Assessment for Treatment Emergent Events – Systematic Inquiry (SAFTEE-SI), the latter two providing information about medication tolerability. These measures and procedures (Measurement Based Care Approach) were successfully used in STAR*D resulting in high-quality care with vigorous but tolerable dosing in both primary and psychiatric settings. All three measures will be collected in the bi-weekly clinic visits. The QIDS-C and the FIBSER will be collected by phone during the four weeks there is no clinic visit (weeks 1, 3, 5, and 7). The phone evaluations of symptom severity and medication tolerability will take approximately 20 minutes. Finally, the first 2 weeks following the initiation of medication and for two weeks after dosage increase (week 4 or later), patients will also be contacted Monday, Wednesday and Friday, via phone and evaluated for the presence of suicidal ideation and the emergence of associated symptoms. These calls will take about 10 minutes. Two of these suicide evaluation phone calls (week one and a week following dosage increase) will also include the symptom severity and medication tolerability assessments (total call time will be approximately 30 minutes). There will therefore be a total of 14 calls—two 20 minute calls, ten 10 minute calls and two 30 minute calls.

Patients will be paid $60 for the initial study visit, and, after the initial visit, subjects will be paid $60 for the final visit. They will also be paid $25 a week for the four weeks in which three suicidal ideation assessment phone calls per week are held. All research procedures are conducted at no cost to the patient. Study medications are considered part of standard care and will be distributed in the manner typically used at each study site.

An overview of key study procedures is in Appendix III. Copies of all study instruments are in Appendix IV.

SCHEMA

Here is the flow of patients through the steps of the study:



ELIGIBILITY

We plan to enroll 300 subjects. The patient population will be made up of individuals of mixed ethnic and socioeconomic backgrounds. Patients will not be excluded due to prior or current co-morbid general medical or psychiatric diagnoses (with the exception of pre-specified exclusion criteria) in order to study a representative population. Patients meeting entrance criteria will be offered the opportunity to participate. Patients will not be excluded on the basis of gender or race.

CRITERIA FOR INCLUSION OF SUBJECTS

- Patients must be enrolled at the primary or specialty care site, and be planning to continue living in the area of that clinic throughout the study
- Patients must be 18-75 years old
- Patients must meet clinical criteria for MDD, based on the PDSQ and DSM IV MDD checklist
- Screening HAM-D_{17} score ≥ 14
- Patients must give written informed consent
- Patients with and without current suicidal ideation may be included in the study
- Patients must not have taken antidepressant medication for at least 2 weeks prior to screen (or 4 weeks in the case of fluoxetine or 6 weeks for MAOI's).

CRITERIA FOR EXCLUSION OF SUBJECTS

- Current substance abuse or dependence
- Two past SSRI treatment failures within the current episode, or last 2 years if chronic.
- Patients with a current Axis I diagnosis of Bipolar disorder or Schizophrenia
- Patients with a current Primary Axis I diagnosis of Obsessive-Compulsive disorder, Anorexia Nervosa or Bulimia.
- Women who are sexually active and who are not using adequate contraception, or who are pregnant, trying to become pregnant, or breast feeding.
- Patients with general medical conditions that contraindicate antidepressant medications
- Patients whose clinical status requires inpatient treatment at the time of baseline interview.
- Patients who cannot read and understand English since all research instruments are not yet translated and validated in Spanish or other languages.
- Some reports of SSRI-induced akathisia-like states have found them to be more highly correlated with either concurrent or previous treatment with a neuroleptic, even in patients with no history of movement disorders therefore, patients who have taken an anti-psychotic medication within 4 months of the screening visit will be excluded from the study.

SCHEDULE OF ASSESSMENTS

		WEEKS										
INSTURMENT	SCREEN	0 BASELINE VISIT	0-2 PHONE MWF	1* PHONE	2 VISIT	3 PHONE	4 VISIT	4-6** PHONE MWF	5* PHONE	6 VISIT	7 PHONE	8 VISIT
CONSENT	CRC											
CLINICAL INTERVIEW	CRC											
MDDC	CRC											
PDSQ	P											
$HRSD_{17}$	CRC											
DEPRESSIVE SEVERITY												
$QIDS\text{-}C_{16}$		CRC		CRC	CRC	CRC	CRC		CRC	CRC	CRC	CRC
SUICIDALITY												
MSSI		CRC					CRC					CRC
PANSI		P			P		P			P		P
SRS		P & CRC	CRC		P		P	CRC		P		P
ASSOCIATED SYMPTOMS												
BARS		CRC			CRC		CRC			CRC		CRC
BAI		P			P		P			P		P
CARS-M		CRC			CRC		CRC			CRC		CRC
IRS		CRC			CRC		CRC			CRC		CRC
PS		CRC			CRC		CRC			CRC		CRC
SRS-AS		P & CRC	CRC		P		P	CRC		P		P
SUBSTANCE USE												
ADQ		CRC			CRC		CRC			CRC		CRC
SIDE EFFECTS												
FIBSER				CRC	P	CRC	P		CRC	P	CRC	P
SAFTEE-SI		P			P		P			P		P
PHYSICAL SYMPTOMS												
SCQ		P										
STUDY RETENTION												
SPQ		P			P		P			P		

*Week 1 and 5 phone assessments will be collected on the closest MMF call of the corresponding week.
**or weeks 6-8 if dosage increase occurs at week 6.
ADQ = Alcohol and Drug Questionnaire
BAI = Beck Anxiety Inventory
BARS = Barnes Akathisia Rating Scale
CARS-M = Clinician Administered Rating Scale for Mania
Consent = Informed Consent
Clinical Interview = Demographics, medical and psychiatric history
CRC = Clinical Research Coordinator
FIBSER = Frequency, Intensity, and Burden of Side Effects Rating
$HRSD_{17}$ = Hamilton Rating Scale for Depression - 17 item
IRS = Impulsivity Rating Scale
MDDC = DSM-IV Major Depressive Disorder Checklist
MWF = Monday, Wednesday, Friday administration
MSSI = Modified Scale of Suicidal Ideation
PDSQ = Psychiatric Diagnostic Screening Questionnaire
P = Patient
PANSI = Positive and Negative Suicide Ideation Inventory
PS= psychosis screen
$QIDS\text{-}C_{16}$ = 16-item Quick Inventory of Depressive Symptomatology – Clinician Rated
SAFTEE-SI = Systematic Assessment for Treatment Emergent Events – Systematic Inquiry
SCQ = Self-administered Comorbidity Questionnaire
SPQ = Study Participation Questionnaire
SRS = Suicidality Rating Scale
SRS-AS = Suicidality Rating Scale - Associated Symptoms

SOURCES OF RESEARCH MATERIAL

Sources of data will include medical records and physician diagnostic evaluation to determine study eligibility, and clinician and patient ratings. These data will be obtained by Clinical Research Coordinators (CRCs), physicians, and the patients for clinical and research purposes. To aid in the identification of patients in need of further evaluation, study physicians may have patients fill-out the PHQ-2 as part of the normal clinic procedure. Potential study patients will also be identified via the physicians' normal clinical interview. During the screening visit, the PDSQ, medical history, patient and family psychiatric history, demographic information, $HRSD_{17}$, and MDDC will be collected to determine eligibility. A $HRSD_{17}$ score of 14 or higher is required for entry into the study. At baseline and weeks 2, 4, 6, and 8 the CRC will collect clinician-rated and patient self-report data in the clinic (see Schedule of Assessments). At weeks 1, 3, 5, and 7 the CRC will collect medication monitoring data ($QIDS\text{-}C_{16}$, FIBSER) via phone contact. During the first 14 days after medication initiation (weeks 1 and 2) and dose increase (weeks 5 and 6 or later) the CRC will evaluate suicidal ideation and associated features (SRS, SRS-AS) via phone contact.

Prescreen Assessments (Optional).

Patient Health Questionnaire - 2 (PHQ-2):[118] The PHQ-2 is a 2-item screen previously validated in primary care. The instrument assesses depressed mood and anhedonia. The construct and criterion validity of this questionnaire make it an attractive and simple measure for depression screening. Rated on a 0 (not at all) to 3 (nearly every day) basis, the self-report questionnaire asks respondents to assess their interest or pleasure and subjective level of depression or hopelessness as it has been over the past two weeks.

Screening Assessments

Hamilton Rating Scale for Depression ($HRSD_{17}$): The $HRSD_{17}$ is a 17-item clinician rated assessment of depressive severity. Scores range from 0 to 52 with higher scores associated with increased levels of depressive severity.

Major Depressive Disorder Checklist (MDDC): This is a brief clinician rated diagnostic scale based upon the Diagnostic and Statistical Manual of Mental Disorders criteria for Major Depressive Disorder (MDD). The scale comprehensively covers the diagnostic criteria for MDD and assess functional impairment and differential diagnosis for MDD due to a medical condition, or due to the effects of a substance.

Psychiatric Diagnostic Screening Questionnaire (PDSQ): PDSQ is patient self report assessment consisting of 125 yes-or-no items, which require approximately 15 to 20 minutes to complete. The scale has a global indicator of psychopathology, and provides diagnostic information for the following DSM-IV Axis I disorders: Major Depressive Disorder, Generalized Anxiety Disorder, Panic Disorder, Posttraumatic Stress Disorder, Alcohol Abuse/Dependence, Drug Abuse/Dependence, Psychosis, Bulimia/Binge-Eating Disorder, Somatization Disorder, Obsessive-Compulsive Disorder, Social Phobia, Hypochondriasis, Agoraphobia.

Measures of Depressive Severity

Quick Inventory of Depressive Symptomatology - Clinician rated ($QIDS\text{-}C_{16}$): This clinician rated 16 item measure derived from the $IDS\text{-}C_{30}$ assesses the 9 DSM symptom criteria for a major depressive episode. This measure has been utilized as the principal instrument driving the critical decision points for the algorithmic pharmacotherapy of several large multi-center trials such as Research Evaluating the Validity of Augmenting Medication with Psychotherapy (REVAMP) (1UO1MH61562) and STAR-D (NO1MH90003).

Measures of Suicidal Ideation

The Modified Scale of Suicidal Ideation (MSSI):[148] The MSSI is an 18-item clinician-administered scale that monitors intensity of ideation, courage and competence to attempt, and talk and writing about death over the past year. The first 4 items have been designated as screening items to identify those individuals whose suicide ideation is severe enough to warrant the administration of the entire scale. Each item is rated on a 0-3 point scale, and the ratings are summed to yield a total score ranging from 0 to 54.

Positive and Negative Suicide Ideation Inventory (PANS):[126] This is a 20-item self-report measure of positive and negative thoughts related to suicide attempts. The inventory consists of two scales, Positive Ideation and Negative Ideation.

Suicidality Rating Scale (SRS): The scale consists of 12 clinician or patient rated items, rated on a fully anchored 5 point Likert scale with responses ranging from 1 (strongly disagree) to 5 (strongly agree).

Measures of Associated Symptoms

Barnes Akathisia Rating Scale (BARS):[131] The clinician rated Barnes Akathisia Rating Scale incorporates diagnostic criteria for pseudoakathisia, and mild, moderate, and severe akathisia. It is a clinician-administered instrument comprising 5 items for rating the observable, restless movements, the subjective awareness of restlessness, and associated distress. In addition, there is an item for rating global severity. A standard examination procedure is recommended.

Beck Anxiety Inventory (BAI):[203] The BAI is a 21 item patient self report of physiologic hyperarousal and cognitive anxiety. The BAI uses a 0 to 3 point scale (not at all to severely) to rate anxiety symptoms over the last week.

Clinician Administered Rating Scale for Mania (CARS-M):[204] The CARS-M is a 15 item clinician rated assessment of symptoms associated with mania occurring during the past week. The CARS-M uses a 0 to 5 point scale, and provides independent indexes for mania and for psychosis.

Impulsivity Rating Scale (IRS):[205] The IRS is a 7 item clinician rated assessment of impulsivity. The IRS uses a 0 to 3 scale to rate irritability, impatience, decision making, distractibility, aggressiveness, response control, and delayed gratification.

Psychosis Screen. This is a 6 item clinician rated psychosis screen based upon the DSM-IV-TR definition of psychosis. The rating scale assesses the presence of hallucinations (auditory, visual), and delusions (persecution, grandiose, somatic, guilt) during the last 2 weeks.

Suicidality Rating Scale - Associated Symptoms (SRS-AS): This clinician or patient rated scale consists of 17 items, rated on a fully anchored 5 point Likert scale with responses ranging from 1 (strongly disagree) to 5 (strongly agree).

Substance Abuse

Alcohol and Drug Questionnaire (ADQ): The ADQ is an 8 item clinician rated scale used to rate alcohol, drug, and tobacco use during the last 2 weeks.

Medication Side Effects

Frequency, Intensity, and Burden Side Effects Rating (FIBSER): This self report provides 3 global ratings each on a Likert-type scale rated 0-6. One rates frequency, another intensity, and the third estimates the overall burden or degree of interference in day-to-day activities and function due to the side effects attributable specifically to the antidepressant treatment.

Systematic Assessment for Treatment Emergent Events-Specific Inquiry (SAFTEE-SI):[24, 25] This is an easy to use 55-item self-report that rates most commonly reported side effects expected with the study medications. This measure will be used to describe side effects associated with protocol treatment.

Medical Comorbidities

Self-administered Comorbidity Questionnaire (SCQ): The SCQ is a 40 item self-report, which assesses the presence of a range of common medical conditions, their severity, and the whether or not the conditions limit function (e.g., heart disease, high blood pressure, lung disease, diabetes, ulcer or stomach disease, etc.).

Measure of Retention

Study Participation Questionnaire (SPQ): The SPQ is a 4-item self report measure which asks for the patient's likelihood of returning for the next visit and completing the study. It also asks for the patient's likelihood of remaining in the study in the context of lack of efficacy or side effects.

Copies of study instruments are in Appendix IV.

Data will be entered into the database by the use of subject identification numbers, and records will be kept confidential. All research staff will be trained in the policies and procedures for protecting human subjects in research, as specified by the National Institutes of Health.

RECRUITMENT OF SUBJECTS

We plan to enroll 300 subjects, up to 30 at each of 15 sites. Potential subjects will be self or professionally referred and seen in psychiatric or primary care clinics. Pre-screening can be done in a telephone or face to face interview with a CRC or a study physician. If it is determined that the patient meets initial study criteria, which includes being prescribed one of the SSRI antidepressant medications designated in this protocol, the CRC will explain the study protocol, offer the informed consent for the patient's review, and if the patient agrees, will obtain written consent. The patient will then be screened for eligibility based on the inclusion/exclusion criteria. Each RC will identify a clinical site which will service all the patients seen at the Regional Center for the study.

We will attempt to include participants with a range of age, race, ethnicity, and socio-economic status. All participants must be English speaking since all research instruments are not yet translated and validated in Spanish or other languages.

The requirements for participating in this project will be reviewed with the patient by the CRC or physician, at which time verbal and written informed consent will be obtained. The consent form will have been approved by the Institutional Review Board (IRB) of each of the institutions.

Other Patient Screening Procedures and procedures for Obtaining Informed Consent are in Appendix III.

TREATMENT

This is an open label non-randomized medication trial in which all patients will take one of six SSRIs (citalopram, escitalopram, sertraline, paroxetine, paroxetine-CR and fluoxetine) at the discretion of the study physician. At baseline and weeks 2, 4, 6, and 8 (5 visits), the patient will be seen first by the CRC and then the physician. The baseline visit will take up to two hours, with the follow-up visits (weeks 2, 4, 6 and 8) taking up to 1 hour. The patient will provide information about progress and side effects through self rated instruments as well as by responding to questions from the CRC and physician who will complete clinician rated instruments (see Appendix IV for instruments). During the visit, the physician will also evaluate for the presence of any other adverse or serious adverse events (e.g., suicidality), and follow the procedures in Appendix III.

The physician will make treatment decisions guided by symptom ratings and side effect frequency, intensity, and burden, and tolerability, utilizing the measurements obtained at each visit, the General Principles for Treatment Implementation (Appendix I), and the Critical Decision Points/Dosing Table (Appendix II). The goal of treatment is remission of symptoms of depression. Further description of other treatment procedures are contained in Appendix III.

EVALUATION CRITERIA

The presence of MDD will be evaluated using the PDSQ and MDDC.

Depressive symptom severity will be evaluated using the QIDS-C_{16}.

Suicidal ideation will be assessed using the MSSI, PANSI, and SRS.

Associated features will be evaluated using the BARS, BAI, CARS-M, IRS , PS and SRS-AS.

Substance use will be assessed using the ADQ.

Medication side effects and tolerability will be assessed using the FIBSER and SAFTEE-SI.

Medical comorbidities will be identified using the SCQ and clinical interview.

Likelihood of retention will be evaluated using the SPQ.

STUDY TERMINATION CRITERIA

There are a number of reasons patients may terminate early from the study.

1. Physician Discretion: Patients deem a potential danger to self or others.

2. Patient Choice: Patients may choose not to continue in the study. CRCs will work with the physician to understand reasons for this choice and offer reasonable support and treatment alternatives to the patient. However, some patients will choose to discontinue participation.

3. Patient Lost to Follow Up: If a patient has missed visits and the CRC is unable to contact the patient, the patient is considered "Lost to Follow Up".

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

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

POTENTIAL RISKS

The primary risk of major depressive disorder is attempting or completing suicide. Occasionally some discomfort may occur while filling out questionnaires or being interviewed about matters pertaining to mood, functioning and other experiences. Those referred for a medical exam, which will be based on clinician judgment, may experience mild discomfort during blood drawing for laboratory tests.

Although, the study medications have been approved by the FDA for human use in patients with MDD, these medications involve the risk of side effects.

Commonly observed side effects include:

Escitalopram. Information about known problems is based upon the experiences of 715 men and women with MDD who have participated in past research using escitalopram (PDR 2005).

In past research, 6% to 15% of people had these problems: nausea (15%), insomnia (9%), sexual dysfunction (9%), diarrhea (8%), dry mouth (6%), increased sleep (6%).

2% to 5% of people had these problems: increased sweating (5%), dizziness (5%), flu like symptoms (5%), fatigue (5%), inflammation of the nose (5%), nasal congestion (3%), constipation (3%), indigestion (3%), appetite decrease (3%), decreased sex drive (3%), abdominal pain (2%).

Citalopram. Information about known problems is based upon the experiences of 1063 men and women with MDD who have participated in past research using citalopram (PDR 2005).

In past research, 6% to 21% of people had these problems: nausea (21%), dry mouth (20%), increased sleep (18%), insomnia (15%), increased sweating (11%), diarrhea (8%), tremor (8%), sexual dysfunction (6%).

2% to 5% of people had these problems: dizziness (5%), flu like symptoms (5%), fatigue (5%), nasal congestion (5%), anxiety (4%), appetite decrease (4%), vomiting (4%), agitation (3%), dysmenorrhea (3%), abdominal pain (3%), sinus infection (3%), impotence (3%), decreased sex drive (2%), fever (2%), joint pain (2%), muscle pain (2%), yawning (2%).

Sertraline. Information about known problems is based upon the experiences of 861 men and women with MDD who have participated in past research using sertraline (PDR 2005).

In past research, 6% to 26% of people had these problems: nausea (26%), diarrhea (18%), insomnia (16%), dry mouth (16%), increased sleep (13%), dizziness (12%), tremor (11%), fatigue (11%), constipation (8%), increased sweating (8%), sexual dysfunction (7%),agitation (6%).

2% to 5% of people had these problems: appetite decrease (3%), abdominal pain (2%).

Paroxetine. Information about known problems is based upon the experiences of 421 men and women with MDD who have participated in past research using paroxetine (PDR 2005).

In past research, 6% to 26% of people had these problems: nausea (26%), increased sleep (23%), headache (18%), dry mouth (18%), muscle weakness (15%), constipation (14%), dizziness (13%), insomnia (13%), sexual dysfunction (13%), diarrhea (12%), increased sweating (11%), decreased appetite (6%).

2% to 5% of people had these problems: anxiety (5%), nervousness (5%), yawning (4%), numbness (4%), blurred vision (4%), gas (4%), palpitations (3%), vasodilatation (3%), decreased sex drive (3%), abnormal vision (2%), muscle aches (2%), rash (2%), taste abnormalities (2%), sedation (2%).

Paroxetine-CR. Information about known problems is based upon the experiences of 212 men and women with MDD who have participated in past research using paroxetine-CR (PDR 2005).

In past research, 6% to 27% of people had these problems: headache (27%), sexual dysfunction (26%), nausea (22%), increased sleep (22%), diarrhea (18%), insomnia (17%), dry mouth (15%), dizziness (14%), fatigue (14%), constipation (10%), infection (8%) abdominal pain (7%), gas (6%), tremor (7%), decreased sex drive (6%), increased sweating (6%).

2% to 5% of people had these problems: yawning (5%), back pain (5%), abnormal vision (5%), sinus congestion (4%), appetite decrease (4%), muscle tension (3%), pain (3%), urinary tract infection (3%), allergic reaction (2%), flushing (2%), vomiting (2%), numbness (2%), agitation (2%), cough increase (2%), numbness (2%), photo sensitivity (2%), menstrual disorder (2%), vaginitis (2%), taste abnormalities (2%).

Fluoxetine. Information about known problems is based upon the experiences of 1728 men and women with MDD who have participated in past research using fluoxetine (PDR 2005).

In past research, 6% to 21% of people had these problems: nausea (21%), insomnia (16%), nervousness (14%), increased sleep (13%), anxiety (12%), diarrhea (12%), appetite decrease (11%), dry mouth (10%), tremor (10%), fatigue (9%), increased sweating (8%).

2% to 5% of people had these problems: rash (4%), decreased sex drive (3%), sore throat (3%), flu syndrome (3%), flushing (3%), sexual dysfunction (2%).

Additional risks with participation in the study include lack of positive response to medication or worsening of depressive symptoms, if the treatment does not lead to adequate improvement.

SPECIAL PRECAUTIONS AND STUDY MONITORING

Despite the occurrence of paradoxical effects during SSRI pharmacotherapy, it is widely acknowledged that there are more suicide-related risks associated with untreated depression than emerge as a result of antidepressant pharmacotherapy. In this study, participating patients are exposed to medications they would routinely be prescribed in doses that are routine in clinical practice and for a duration of time that mirrors consensually-recommended preferred practices. As such, this protocol is consistent with standard care. Therefore, study-related risks are considered to be no greater than usual clinical care. In fact, because of the use of the study treatment algorithm and close monitoring, it may be argued that the risks are less than for treatment as usual. For these reasons, study-related human subject risk is considered to be minimal.

There are two types of contacts during which time increased suicidal risk can be identified: 1) at the time of study visits, and 2) during phone assessments or a phone call. Prior to study implementation, each Regional Center will provide to the Principal Investigator a copy of risk management procedures for this study for clinic and phone-based patient contacts based on their selected clinic's specific crisis management requirements. All Regional Centers' risk management procedures will be reviewed and approved by the Depression Trial Network's Network Management Committee which includes the Principal Investigator and the scientific and

operational leadership of the Depression Trials Network.

Risk management procedures typically include the following: Patients who report risk of self-harm at any point of contact will be thoroughly evaluated by the CRC for intent, plan and means for suicide. If the patient is in the clinic, the physician will be immediately notified to further assess the patient. If the patient is deemed an acute risk for suicide, the physician will direct the measures necessary to get the patient to safety, using clinic specific crisis management procedures. If the CRC identifies that the patient may be at acute risk during a phone assessment, a complete evaluation of the situation is necessary. For example, if the patient indicates thoughts of suicide/death several times a day in depth on the QIDS-C_{16}, the CRC will obtain information about the patient's intent, plan and means at hand for suicide, as well as determine, as appropriate, the location of the patient and whether anyone else is with the person. Measures to keep the patient safe, including the option of calling 911 for police assistance will be implemented as based on the assessment of risk, and consistent with the clinic's crisis management procedures.

Study staff will report to emergency treatment providers any information relevant to treatment decision-making, including any evidence of suicidality. All serious adverse events will be reported to the Principal Investigator, DTN Safety Officer, and NIMH (via the DCC) within 24 hours of the occurrence. Notice will also be provided to the DSMB, and reported to RC IRBs per institutional policy.

CRCs will be trained prior to study initiation, in the identification and assessment of suicidal risk based on both patient responses to study instruments as well as in depth questioning of patients about current suicidality in either setting. Training will include case scenarios. There will be ongoing opportunities to discuss safety related procedures and individual patient cases in semi-monthly calls with Regional Center Directors, led by the Principal Investigator and semi-monthly calls with CRCs led by the Clinical Manager.

Physical exams may be done if the study physician feels it is necessary (i.e., because of medical history). Other evaluations such as laboratory assessments or an electrocardiogram (ECG) may also be given if the study physician feels they are necessary. A urine pregnancy test (HCG) may be obtained if doubt exists about whether a woman could be pregnant. Any woman who becomes pregnant will be discontinued from the study immediately and referred for appropriate treatment.

Effective treatment, ongoing follow-up and evaluation, and 24-hour telephone coverage will be available to patients to minimize the risk of suicide. When necessary, hospitalization is available. Physician, CRC and Investigator phone numbers are provided, and patients are encouraged to call should they need additional assistance beyond scheduled appointments. The clinicians and CRCs maintain close contact with subjects and reschedule appointments as needed. Either the patient or the physician may discontinue the patients study participation at any time should the patient's symptoms worsen or if the patient simply desires to withdraw. Use of these procedures minimizes risk.

At each visit, the patient will complete a self-report form indicating any side effects to the study treatment. The clinician side effect report will be completed as well. Side effects will also be evaluated by the CRC by phone in weeks without scheduled study visits. Adverse events are explained in Appendix III. All information will be used by the study physician, along with any other pertinent medical information the patient reports. Depression symptoms will be monitored at each visit, with the risk for suicide thoroughly assessed. All data forms completed by the patient will be reviewed for content by the CRC before the patient leaves the clinic. This will ensure that nothing is overlooked in the evaluation process, including any indication of suicidality. All data collected at each visit are reviewed by the CRC and study physician so that monitoring of study data for any risk consistently occurs in real time throughout the study.

The Regional Centers are responsible for reporting, on a data form, any serious adverse event (SAE) that a study patient experiences. These SAE forms are sent to the DCC, and sent on to the Safety Officer for review. The Safety Officer will determine if the event is expected to occur, based on known information about the study medications, and if the event is thought to be related to the study treatment. The Safety Officer can make recommendations to the Regional Center for follow-up action. Definition of and procedures for reporting Serious Adverse Events are detailed in Appendix III.

There is also oversight by the DTN Data Safety and Monitoring Board (DSMB) for safe conduct of the study. The DSMB will review the protocol and consent documents prior to study initiation. The DSMB will monitor safety issues, including the review of adverse events; the adequacy and integrity of accumulating data; and the study's capabilities to meet its objectives. The DSMB will approve study initiation, and monitor subject enrollment, and determine if study procedures should be altered or stopped because of evidence of benefit or harm to trial subjects that may be attributable to the intervention under evaluation or reasons related to scientific integrity. The DSMB will conduct independent and objective reviews of all accumulated data from the pilot trial. The NCC and DCC respond to all DSMB issues and queries and ensure that all DSMB actions and correspondences are submitted to local IRBs throughout the study as needed.

PROCEDURES TO MAINTAIN CONFIDENTIALITY

Investigators will take all possible precautions to protect patient confidentiality. CRCs will enter data by coded subject identification numbers, and records will be kept in locked filing cabinets at Regional Centers/Clinical Sites. No subjects will be identified by name in publications. Any information that is obtained in connection with research that can be identified with a subject will remain confidential and can be disclosed only with a subject's explicit, properly informed written consent. Copies of executed consent forms are stored on site in locked filing cabinets at the Regional Centers/Clinical Sites. Patients will be advised that representatives of the FDA, Sponsor and the IRB may review their medical and research records to assure the quality of information used in the research.

Research data collected at the Regional Centers/Clinical Sites will be sent to the Epidemiology Data Center of the University of Pittsburgh's Graduate School of Public Health (DCC), for the purposes of data analysis. No personal identifying information such as names, social security numbers, medical record numbers, or insurance ID numbers will be sent to the DCC. Only a code number will be used to identify all data. Research data is stored in a secure database.

Subject identifying information (name, address, and social security number) is sent from the Regional Centers to the NCC at The University of Texas Southwestern Medical Center at Dallas for payment purposes. All information is stored in a locked filing cabinet. Personnel processing payments have no access to research data.

To further protect privacy, the NCC will obtain a Certificate of Confidentiality from the National Institutes of Health.

BIOSTATISTICS

The primary aims of the proposed study are designed to develop methodology which will allow us to: a) to collect detailed quantitative descriptions of the possible effects of SSRIs on the processes associated with increased risk for suicide, and b) to measure the extent to which these processes are impacted by SSRI treatment.

Specific Aim 1: The goal of this aim will be to psychometrically evaluate the SRS and the SRS-AS. This will include the assessment of reliability and validity, which are the cornerstones to the psychometric evaluation of an instrument. Several criteria will be used to assess internal consistency. First, inter-item correlations, corrected item-total correlations, and Cronbach's alphas will be calculated. Although no objective cutoffs for these measures exist, alpha's above .7-.8 (when corrected for scale length) are generally considered to be good. Even though overall alpha's may be high, individual items which correlate poorly with overall scale scores may contribute to the unreliability. Thus, examination of inter-item correlation, item-total correlations, and alphas when an item is deleted also will guide the determination of reliability. Second, exploratory factor analysis will

be used to assess the overall reliability and factor structure of psychological measures and will be used to investigate the domains and the internal consistency of the measures. Additional assessment of convergent and discriminant validity will be conducted. Lastly, item response theory will be used to generate a translation of the scores of the SRS to scores of standard suicide measures.

Specific Aim 2: The feasibility of the proposed approach will be evaluated by examining the frequency of missing data in terms of missing items on the suicide measures, missed visit and study terminations. For each, the proportion of missing will be assessed and 95% confidence intervals will be estimated.

Specific Aim 3: Using the proposed sample of 300, a significant increase in suicidal ideation in 5 to 10 percent of the patient sample allows for such effects to be seen in 15 to 30 patients. This number should be sufficient to estimate possible relationships between any associated effects and increased or new onset suicidal ideation. In the event that there are moderate to large[165] correlations between suicidal ideation and associated effects (i.e., impulsivity, akathisia, activation, hopelessness), the current sample size will allow for direct tests of these relationships. In this case, analyses will be conducted using a series of random regression models. These models will be constructed to evaluate the time-dependent changes in these associated effects and suicidal ideation. Like survival analysis, the weighted least squares (WLS) and generalized estimating equations (GEE) analyses can use subjects with missing data that would have to be dropped from repeated measures ANOVA models. One advantage of the random regression model is it is more robust for missing data. This analysis will be designed to find the best predictors of increasing suicidal ideation so that the measures can be constructed to help monitor the patients more at risk.

POTENTIAL BENEFITS

Benefits include the possibility of participants' relief from symptoms of major depressive disorder. The direct benefit to the patients may be small or nothing, but what is learned from this study could help people with major depressive disorder in the future.

RISK BENEFIT ASSESSMENT

Suicide rates across the world have not been significantly impacted by decades of research and substantial advances in the treatment of depression. Partially for this reason, in 1999, the former Surgeon General of the United States and the former Director-General of the World Health Organization both identified suicide prevention as an area of high priority, and specifically promoted initiatives that would fund additional suicide-related research. In addition, as mentioned above, research clearly shows that not treating patients with MDD places them at greater risk of suicidal states than the risk from medications. Given that recruitment, and biweekly medication management visits take place in clinical settings accustomed to handling emergencies and with excellent access to emergency care, patient risk during these occasions will generally be well controlled. Emergent or increased levels of suicidality outside of these structured visits will be evaluated with phone calls three times a week after dose initiation and increase and weekly assessments in the remaining weeks where there is no clinic visit. Emergency intervention will be consistently initiated as needed. Our previous experience with the usual treatment of MDD suggests that our study patients have an opportunity for enhanced benefit during treatment of MDD, since treatment of depression as defined by the study protocol results in improved outcomes.

The potential benefit is the discovery of an effective method for monitoring suicidal thinking from the onset of treatment with an antidepressant medication . All research procedures are conducted at no cost to the patient.

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APPENDIX I

GENERAL PRINCIPLES FOR TREATMENT IMPLEMENTATION

- If possible the Screening and Baseline evaluation are performed during the same Clinical Visit.
- Critical Decision Points (CDPs) are designed to prompt an assessment of symptoms and a determination of a need for a change in tactics or steps. At each CDP, the physician should 1) assess the severity of the patient's symptoms with the QIDS-C_{16} and determine if an increase in medication is appropriate (in cases of Mild or No improvement), 2) assess the patient for tolerance with the FIBSER, and SAFTEE-SI and make a decision to either continue or change treatment based on the patient's ability to tolerate the medication.
- Patients not responding to medication, as evidenced by QIDS-C_{16} scores of 9 or above, will have their medication increased until maximum dosages are reached, assuming side effects are not problematic.
- Patients with QIDS-C_{16} scores ranging from 6 to 8, may have their medication increased or maintained at the same dosage starting at week 2, assuming side effects are not problematic.
- Patients with QIDS-C_{16} scores below 6, may be maintained at the same dosage starting at week 2, assuming side effects are not problematic.
- Patients experiencing intolerable side effects will decrease dose, manage side effects and continue, or exit the study. Patients experiencing tolerable side effects may have the medication dosage decreased, or continue the current dose and manage the side effects.
- Adjunctive medications prescribed for the treatment of associated symptoms such as anxiety or treatment-emergent side effects should be discontinued once these symptoms resolve. The rationale for their use should be carefully documented. The continued indication for these medications should be reassessed on a regular basis.
- Sleep medications may be used at the physicians discretion.
- Anxiolytic medications may be used at the physicians discretion.

APPENDIX II: DOSING TABLE

ESCITALOPRAM

WEEK 0	ESCITALOPRAM
Start patient on Escitalopram 10 mg/day.	
Return to clinic:	Return in 2 weeks.

WEEK 2	ESCITALOPRAM
Continue Escitalopram 10mg.	
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE are not manageable.
Return to clinic:	Return in 2 weeks.

WEEK 4	ESCITALOPRAM
***Symptom Improvement** (SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Escitalopram to 20 mg/day.
QIDS-$C_{16} = 6\text{-}8$	Increase Escitalopram to 20 mg/day *or* Continue current dose.
QIDS-$C_{16} \leq 5$	Continue current dose.
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE are not manageable.
Return to clinic:	Return in 2 weeks.

*Use the FIBSER and SAFTEE-SI as a guide.

WEEK 6	ESCITALOPRAM
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Escitalopram to 20 mg/day.
QIDS-$C_{16} = 6\text{-}8$	Increase Escitalopram to 20 mg/day *or* Continue current dose.
QIDS-$C_{16} \leq 5$	Continue current dose.
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE are not manageable.
Return to clinic:	Return in 2 weeks.

WEEK 8	ESCITALOPRAM
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Exit Study
QIDS-$C_{16} = 6\text{-}8$	Exit Study
QIDS-$C_{16} \leq 5$	Exit Study
SEs are significant*	Exit Study
SEs are intolerable*	Exit Study
Return to clinic:	As Needed

*Use the FIBSER and SAFTEE-SI as a guide.

CITALOPRAM

WEEK 0	CITALOPRAM
Start patient on Citalopram 20 mg/day.	
Return to clinic:	Return in 2 weeks.

WEEK 2	CITALOPRAM
Continue Citalopram 20 mg/day.	
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE are not manageable.
Return to clinic:	Return in 2 weeks.

WEEK 4	CITALOPRAM
***Symptom Improvement** (SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Citalopram to 40 mg/day.
QIDS-$C_{16} = 6\text{-}8$	Increase Citalopram to 40 mg/day *or* Continue current dose.
QIDS-$C_{16} \leq 5$	Continue current dose.
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE are not manageable.
Return to clinic:	Return in 2 weeks.

*Use the FIBSER and SAFTEE-SI as a guide.

WEEK 6	CITALOPRAM
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Citalopram to 40 mg/day.
QIDS-$C_{16} = 6\text{-}8$	Increase Citalopram to 40 mg/day *or* Continue current dose.
QIDS-$C_{16} \leq 5$	Continue current dose.
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE are not manageable.
Return to clinic:	Return in 2 weeks.

WEEK 8	CITALOPRAM
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Exit Study
QIDS-$C_{16} = 6\text{-}8$	Exit Study
QIDS-$C_{16} \leq 5$	Exit Study
SEs are significant*	Exit Study
SEs are intolerable*	Exit Study
Return to clinic:	As Needed

*Use the FIBSER and SAFTEE-SI as a guide.

SERTRALINE

WEEK 0	SERTRALINE
Start patient on Sertraline 50 mg/day.	
Return to clinic:	Return in 2 weeks.

WEEK 2	SERTRALINE
Increase Sertraline to 100 mg/day.	
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE are not manageable.
Return to clinic:	Return in 2 weeks.

WEEK 4	SERTRALINE
***Symptom Improvement** (SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Sertraline to 150 mg/day.
QIDS-$C_{16} = 6\text{-}8$	Increase Sertraline to 150 mg/day *or* Continue current dose.
QIDS-$C_{16} \leq 5$	Continue current dose.
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE are not manageable.
Return to clinic:	Return in 2 weeks.

*Use the FIBSER and SAFTEE-SI as a guide.

WEEK 6	SERTRALINE
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Sertraline to 150 mg/day.
QIDS-$C_{16} = 6$-8	Increase Sertraline to 150 mg/day *or* Continue current dose.
QIDS-$C_{16} \leq 5$	Continue current dose.
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE are not manageable.
Return to clinic:	Return in 2 weeks.

WEEK 8	SERTRALINE
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Exit Study
QIDS-$C_{16} = 6$-8	Exit Study
QIDS-$C_{16} \leq 5$	Exit Study
SEs are significant*	Exit Study
SEs are intolerable*	Exit Study
Return to clinic:	As Needed

*Use the FIBSER and SAFTEE-SI as a guide.

PAROXETINE

WEEK 0	PAROXETINE
	Start patient on Paroxetine 20 mg/day.
Return to clinic:	Return in 2 weeks.

WEEK 2	PAROXETINE
	Continue Paroxetine 20 mg/day.
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE are not manageable.
Return to clinic:	Return in 2 weeks.

WEEK 4	PAROXETINE
***Symptom Improvement** (SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Paroxetine to 40 mg/day.
QIDS-$C_{16} = 6$-8	Increase Paroxetine to 40 mg/day *or* Continue current dose.
QIDS-$C_{16} \leq 5$	Continue current dose.
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE are not manageable.
Return to clinic:	Return in 2 weeks.

*Use the FIBSER and SAFTEE-SI as a guide.

WEEK 6	PAROXETINE
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Paroxetine to 40 mg/day.
QIDS-C_{16} = 6-8	Increase Paroxetine to 40 mg/day *or* Continue current dose.
QIDS-$C_{16} \leq 5$	Continue current dose.
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE are not manageable.
Return to clinic:	Return in 2 weeks.

WEEK 8	PAROXETINE
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Exit Study
QIDS-C_{16} = 6-8	Exit Study
QIDS-$C_{16} \leq 5$	Exit Study
SEs are significant*	Exit Study
SEs are intolerable*	Exit Study
Return to clinic:	As Needed

*Use the FIBSER and SAFTEE-SI as a guide.

PAROXETINE-CR

WEEK 0	PAROXETINE-CR
Start patient on Paroxetine-CR 25 mg/day.	
Return to clinic:	Return in 2 weeks.

WEEK 2	PAROXETINE-CR
Continue Paroxetine-CR 25 mg/day.	
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE are not manageable.
Return to clinic:	Return in 2 weeks.

WEEK 4	PAROXETINE-CR
***Symptom Improvement** (SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Paroxetine-CR to 37.5 mg/day.
QIDS-C_{16} = 6-8	Increase Paroxetine-CR to 37.5 mg/day *or* Continue current dose.
QIDS-$C_{16} \leq 5$	Continue current dose.
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE are not manageable.
Return to clinic:	Return in 2 weeks.

*Use the FIBSER and SAFTEE-SI as a guide.

WEEK 6	PAROXETINE-CR
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Paroxetine-CR to 37.5 mg/day.
QIDS-C_{16} = 6-8	Increase Paroxetine-CR to 37.5 mg/day *or* Continue current dose.
QIDS-$C_{16} \leq 5$	Continue current dose.
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE are not manageable.
Return to clinic:	Return in 2 weeks.

WEEK 8	PAROXETINE-CR
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Exit Study
QIDS-C_{16} = 6-8	Exit Study
QIDS-$C_{16} \leq 5$	Exit Study
SEs are significant*	Exit Study
SEs are intolerable*	Exit Study
Return to clinic:	As Needed

*Use the FIBSER and SAFTEE-SI as a guide.

FLUOXETINE

WEEK 0	FLUOXETINE
Start patient on Fluoxetine 20 mg/day.	
Return to clinic:	Return in 2 weeks.

WEEK 2	FLUOXETINE
Continue Fluoxetine 20 mg/day.	
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE are not manageable.
Return to clinic:	Return in 2 weeks.

WEEK 4	FLUOXETINE
***Symptom Improvement** (SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Fluoxetine to 40 mg/day.
QIDS-$C_{16} = 6\text{-}8$	Increase Fluoxetine to 40 mg/day *or* Continue current dose.
QIDS-$C_{16} \leq 5$	Continue current dose.
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE are not manageable.
Return to clinic:	Return in 2 weeks.

*Use the FIBSER and SAFTEE-SI as a guide.

WEEK 6	FLUOXETINE
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Fluoxetine to 40 mg/day.
QIDS-$C_{16} = 6\text{-}8$	Increase Fluoxetine to 40 mg/day *or* Continue current dose.
QIDS-$C_{16} \leq 5$	Continue current dose.
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE are not manageable.
Return to clinic:	Return in 2 weeks.

WEEK 8	FLUOXETINE
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Exit Study
QIDS-$C_{16} = 6\text{-}8$	Exit Study
QIDS-$C_{16} \leq 5$	Exit Study
SEs are significant*	Exit Study
SEs are intolerable*	Exit Study
Return to clinic:	As Needed

*Use the FIBSER and SAFTEE-SI as a guide.

APPENDIX III: KEY STUDY PROCEDURES

PATIENT SCREENING PROCEDURES

Given the broad range of types of clinical sites, the referral/recruitment procedures at each site will likely be slightly different and should be adapted by the CRC and site staff to fit that site's operations.

PRE-SCREEN

The clinician sees a patient whom he/she believes to be appropriate for the study according to the following criteria:

- Patient has clinically significant depression as judged by the clinician.
- Medication is a clinically appropriate option for the treatment of depression or a change in current medications for the treatment of depression is clinically appropriate.
- Patient is between 18 - 75.
- Patient does not have a history of psychosis, as judged by the clinician.
- Patient does not currently require hospitalization for the treatment of depression or for other medical reasons.
- Patient has no definitive treatment resistance history to the medication under study in the current episode.
- Patient does not require more treatment/care for the depression than is available in the protocol.
- Patient can read and understand English.

OBTAINING INFORMED CONSENT

If the patient meets all the above pre-screen criteria, the clinician will briefly discuss the study with the patient to determine if the patient is interested in participating. If interested, the patient will be seen by the CRC.

If the CRC determines that the patient may be eligible for the study, the CRC will obtain informed consent Prior to study entry and performing any study-related procedures, the CRC must obtain informed consent. If the Informed Consent has been signed, the CRC will administer the measures to determine eligibility.

Before asking the patient to sign the consent form, the CRC:

- Explains the purpose and requirements of the study. It is important that the patient understand the time involved in the increased clinic visits and research outcomes assessments, including the schedule for the telephone assessments.
- Provides the consent form to the patient for the patient to read.
- Reviews the consent form with the patient, going over the major points.
- Asks the patient at the end if s/he has any questions.
- Answers any questions from the patient.

Who can sign the consent forms:

- Patients 18 and older.
- Patients who do not have a guardian.
- The guardian of a patient (with written consent of the patient).

Who cannot sign the consent forms:

Family members may not sign for the patient (unless they have proof of guardianship).
- Patients who have a guardian.

Note: If the patient is excluded from the study or does not sign informed consent. The patient is referred back to the clinician for nonstudy treatment.

CLINIC VISIT PROCEDURES

After signing informed consent and being screened, eligible patients will be seen for treatment and evaluated at Baseline (Week 0), and at Weeks 2, 4, 6, and 8. Medication will be titrated based upon symptom severity (QIDS-C_{16}), and side effect profile (FIBSER and SAFTEE-SI), using the enclosed medication dosing tables. It is recommended that the Screening and Baseline Visits be combined into one clinical visit.

SCREENING VISIT

- Informed Consent
- Clinical Interview (demographics, medical history, patient and family psychiatric history)
- $HRSD_{17}$ = Hamilton Rating Scale for Depression - 17 item
- MDDC = Major Depressive Disorder Checklist
- PDSQ = Psychiatric Diagnostic Screening Questionnaire (optional)

BASELINE CLINIC VISIT

- ADQ = Alcohol and Drug Questionnaire
- BAI = Beck Anxiety Inventory
- BARS = Barnes Akathisia Rating Scale
- CARS-M = Clinician Administered Rating Scale for Mania
- IRS = Impulsivity Rating Scale
- Medication per Dosing Tables
- MSSI = Modified Scale of Suicidal Ideation
- PANSI = Positive and Negative Suicide Ideation Inventory
- PS= Psychosis Screen
- QIDS-C_{16}= 16 item Quick Inventory of Depressive Symptomatology – Clinician rated
- SAFTEE-SI = Systematic Assessment for Treatment Emergent Events-Specific Inquiry
- SCQ = Self-administered Comorbidity Questionnaire
- SPQ = Study Participation Questionnaire
- SRS = Suicidality Rating Scale
- SRS-AS = Suicidality Rating Scale-Associated Symptoms

WEEK 2 CLINIC VISITS

- ADQ = Alcohol and Drug Questionnaire
- BAI = Beck Anxiety Inventory
- BARS = Barnes Akathisia Rating Scale
- CARS-M = Clinician Administered Rating Scale for Mania
- FIBSER = Frequency, Intensity, and Burden Side Effects Rating
- IRS = Impulsivity Rating Scale
- Medication per Dosing Tables
- PANSI = Positive and Negative Suicide Ideation Inventory
- PS= Psychosis Screen
- QIDS-C_{16}= 16 item Quick Inventory of Depressive Symptomatology – Clinician rated
- SAFTEE-SI = Systematic Assessment for Treatment Emergent Events-Specific Inquiry
- SPQ = Study Participation Questionnaire
- SRS = Suicidality Rating Scale
- SRS-AS = Suicidality Rating Scale-Associated Symptoms

WEEK 4 CLINIC VISITS

- ADQ = Alcohol and Drug Questionnaire
- BAI = Beck Anxiety Inventory
- BARS = Barnes Akathisia Rating Scale
- CARS-M = Clinician Administered Rating Scale for Mania
- FIBSER = Frequency, Intensity, and Burden Side Effects Rating
- IRS = Impulsivity Rating Scale
- Medication per Dosing Tables
- MSSI = Modified Scale of Suicidal Ideation
- PANSI = Positive and Negative Suicide Ideation Inventory
- PS= Psychosis Screen
- QIDS-C_{16}= 16 item Quick Inventory of Depressive Symptomatology – Clinician rated
- SAFTEE-SI = Systematic Assessment for Treatment Emergent Events-Specific Inquiry
- SPQ = Study Participation Questionnaire
- SRS = Suicidality Rating Scale
- SRS-AS = Suicidality Rating Scale-Associated Symptoms

WEEK 6 CLINIC VISITS

- ADQ = Alcohol and Drug Questionnaire
- BAI = Beck Anxiety Inventory
- BARS = Barnes Akathisia Rating Scale
- CARS-M = Clinician Administered Rating Scale for Mania
- FIBSER = Frequency, Intensity, and Burden Side Effects Rating
- IRS = Impulsivity Rating Scale
- Medication per Dosing Tables

- PANSI = Positive and Negative Suicide Ideation Inventory
- PS= Psychosis Screen
- QIDS-C_{16}= 16 item Quick Inventory of Depressive Symptomatology – Clinician rated
- SAFTEE-SI = Systematic Assessment for Treatment Emergent Events-Specific Inquiry
- SPQ = Study Participation Questionnaire
- SRS = Suicidality Rating Scale
- SRS-AS = Suicidality Rating Scale-Associated Symptoms

WEEK 8 CLINIC VISIT (STUDY EXIT / EARLY TERMINATION)

- ADQ = Alcohol and Drug Questionnaire
- BAI = Beck Anxiety Inventory
- BARS = Barnes Akathisia Rating Scale
- CARS-M = Clinician Administered Rating Scale for Mania
- FIBSER = Frequency, Intensity, and Burden Side Effects Rating
- IRS = Impulsivity Rating Scale
- Medication per Dosing Tables
- MSSI = Modified Scale of Suicidal Ideation
- PANSI = Positive and Negative Suicide Ideation Inventory
- PS= Psychosis Screen
- QIDS-C_{16}= 16 item Quick Inventory of Depressive Symptomatology – Clinician rated
- SAFTEE-SI = Systematic Assessment for Treatment Emergent Events-Specific Inquiry
- SPQ = Study Participation Questionnaire
- SRS = Suicidality Rating Scale
- SRS-AS = Suicidality Rating Scale-Associated Symptoms

WEEK 1, 2, 5, 6 PHONE EVALUATION - MONDAY, WEDNESDAY, FRIDAY

- SRS = Suicidality Rating Scale
- SRS-AS = Suicidality Rating Scale - Associated Symptoms

Note. If dosage escalation is delayed until the week 6 visit, the MWF calls will also be delayed until weeks 7 and 8, to correspond to the dosage escalation.

WEEK 1, 3, 5, 7 PHONE EVALUATION - (WEEK 1 AND 5 PHONE ASSESSMENTS WILL BE COLLECTED ON ONE OF THE MWF CALLS IN THE CORRESPONDING WEEK)

- FIBSER = Frequency, Intensity, and Burden Side Effects Rating
- QIDS-C_{16} = 16-item Quick Inventory of Depressive Symptomatology – Clinician Rated