RESEARCH PROTOCOL

COMBINING MEDICATIONS TO ENHANCE DEPRESSION OUTCOMES (CO-MED)

DECEMBER 19, 2007

CONTACT INFORMATION FOR COMMENTS

A. John Rush, M.D.
Vice Chair, Department of Clinical Sciences
Professor, Department of Psychiatry
University of Texas Southwestern Medical Center
5323 Harry Hines Blvd., Room E5.506
Dallas, TX 75390-9066
Phone: (214) 648-4832
Fax: (214) 648-6863
E-mail: john.rush@utsouthwestern.edu

Madhukar H. Trivedi, M.D.
Mood Disorders Program & Clinic
Department of Psychiatry
University of Texas Southwestern Medical Center
Exchange Park Express, American General Tower
6363 Forest Park Road, Suite 13.354
Dallas, TX, 75235
Phone: (214) 648-0188
Fax: (214) 648-0167
E-mail: madhukar.trivedi@utsouthwestern.edu

TABLE OF CONTENTS

PURPOSE AND OBJECTIVES

The low remission rates with any initial monotherapy and the modest additional remissions achieved with a subsequent switch or augmentation medication step suggest the potential need of using medication combinations at the outset of treatment of major depressive disorder (MDD). This new treatment paradigm has the potential to increase remission rates by treating a broader spectrum of depressed patients and by capitalizing on additive medication effects.

This study compares three different initial medication treatments (escitalopram alone, escitalopram plus bupropion SR, and venlafaxine XR plus mirtazapine) in the short-term (12 weeks), and the durability of benefits in the longer-term (28 weeks) treatment of chronic and recurrent major depression (CRMD) when used as initial treatments in the current major depressive episode (MDE).

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

SPECIFIC AIM 1

To compare the short-term (12-week) outcomes of escitalopram (S-CIT) with those of bupropion SR plus S-CIT (BUP-SR + S-CIT), and with those of venlafaxine-XR plus mirtazapine (VEN-XR + MIRT) based on symptom remission rates defined by the 16-item Quick Inventory of Depressive Symptomatology – Self-report ($QIDS\text{-}SR_{16}$).[1;2]

SPECIFIC AIM 2

To compare the short-term (12-week) outcomes of these three treatment approaches in terms of other symptoms (e.g., anxiety as assessed by the 30-item Inventory of Depressive Symptomatology – Clinician-rated ($IDS\text{-}C_{30}$);[2-4] function as assessed by the Work and Productivity Inventory (WPAI),[5] Work and Social Adjustment Scale (WSAS),[6] and Quality Of Life Inventory(QOLI);[7] cognitive and physical well-being evaluated with the Cognitive and Physical Functioning Questionnaire (CPFQ); treatment emergent psychiatric symptoms assessed with the Suicidality Rating Scale (SRS) and the Suicidality Rating Scale - Associated Symptoms (SRS-AS); side-effect burden as measured by the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER);[8] specific side effects as gauged by the Systematic Assessment for Treatment Emergent Events-Systematic Inquiry (SAFTEE-SI);[9;10] and attrition.

SECONDARY AIM 1

To compare the three treatment approaches in terms of longer-term, sustained effects (up to 28 weeks) in terms of depressive symptoms ($QIDS\text{-}SR_{16}$).

SECONDARY AIM 2

To compare the three treatment approaches in terms of long-term effects, including symptoms such as anxiety, function, quality of life, cognitive and physical well-being, suicidality and associated psychiatric symptoms, specific side effects and side-effect burden, and attrition.

SECONDARY AIM 3

Exploratory analyses will be conducted to identify potential mediators and moderators of the short-term and longer-term phase outcomes.

OVERVIEW

The overall aim of Combining Medications to Enhance Depression Outcomes (CO-MED) is to enhance remission rates for representative, self-declared outpatients with chronic or recurrent nonpsychotic major depressive disorder (CRMD) defined by DSM-IV TR[11], treated in primary or psychiatric care settings.

Current evidence indicates that remission, the goal of treatment, is found in only about one-third of representative depressed outpatients treated for up to 14 weeks with an initial SSRI. In addition, even for those who do respond or remit, over one-third relapse in the subsequent 12 months. Combinations of antidepressants are used in practice at the second or subsequent steps when relapse occurs in the longer term, or, in some cases, even acutely as a first step when speed of effect is a clinical priority. Such combinations could potentially offer higher remission rates, lower attrition, or greater longer-term benefit if used as initial treatments as compared to monotherapy.

Pilot studies of combinations indicate acceptable tolerability and higher remission rates than expected – specifically with combinations of an SSRI plus bupropion, or mirtazapine plus venlafaxine-XR.

CO-MED will provide a robust proof of concept that two different combinations used in the first treatment step will enhance remission rates, be tolerable, and result in acceptable attrition and provide better sustained benefits in the longer term. If positive, results would likely recommend major revisions in how patients with chronic or recurrent MDD are treated in practice.

We will compare two different medication combinations, each against a monotherapy as a first step medication treatment. The proposed study compares a standard highly selective serotonin reuptake inhibitor (SSRI), escitalopram (S-CIT), a broader-spectrum combination (BUP-SR + S-CIT), and a combination that acts by a wider range of different mechanisms (beyond reuptake inhibitor) but that targets both norepinephrine (NE) and serotonin (5HT) systems (VEN-XR + MIRT).

Following written informed consent, participants will be seen by a study clinician for a screening evaluation. Eligible participants will be randomly assigned to treatment with either a combination of escitalopram (open) and placebo (blinded), bupropion SR (open) and escitalopram (blinded), or venlafaxine XR (open) and mirtazapine (blinded), during a 12-week, short-term phase. Note that the first medication will be open label and the second will be single blind (the participant will not know what the second medication is, but the study staff will). The blinding will be maintained throughout the entire 28-week study. In all, 660 adult participants with CRMD, between the ages of 18 and 75, will be enrolled at 15 primary and specialty care sites across the USA. We expect approximately 975 patients will sign consent and be screened to enroll 660 eligible participants into the study. Broadly inclusive entry criteria will be used.

BACKGROUND

Major depressive disorder (MDD) is a serious, debilitating, life-shortening illness that affects many persons of all ages and backgrounds (point prevalence = 2.3%-3.2% in men; 4.5%-9.3% in women; lifetime risk = 7-12% for men and 20-25% for women[12]). Over 50% of patients who suffer a single major depressive episode (MDE) will eventually develop another.[13;14] Most depressed patients have a recurrent or chronic course with either prolonged episodes or substantial interepisode symptomatology and disability.[15-17] Chronic/recurrent depression (CRMD) includes: 1) double depression, 2) chronic MDD, and 3) recurrent MDD with complete

or incomplete interepisode recovery. Double depression, the coexistence of dysthymic disorder with superimposed MDEs, is common among patients with dysthymic disorder (75%).[18-20] At least 25% of patients with MDD in practice also have dysthymic disorder.[21] DSM-IV TR designates chronic MDD when the MDE lasts at least 2 years. Recurrent MDD with complete interepisode recovery refers to MDD patients who are asymptomatic between MDEs, but many MDD patients do not fully remit between episodes.[20;22] Recurrent MDD, especially with incomplete interepisode recovery, is often associated with early onset (first MDE before ages 18-25).[23]

At least 50% of patients[23;24] with MDD have chronic episodes, double-depression,[20;25] or recurrent episodes with significant interepisode symptomatology.[20] Recent epidemiological studies indicate that 3-6% of persons in the community suffer from some form of chronic depression.[26] These patients, while very common in clinical practice, are often excluded from efficacy trials.[27;28] Patients with double depression, chronic MDD, and recurrent MDD with incomplete interepisode recovery have similar demographic and clinical characteristics, family history, and treatment response.[29-33]

The paradigm of using combination treatments is analogous to treatment for other severe general medical conditions (e.g., cancer, congestive heart failure, malignant hypertension, HIV, etc.). That is, more vigorous initial treatment efforts are implemented initially, rather than using an extended trial-and-error, multistep approach to isolate the single best medication or combination. If positive, results of the proposed study would dramatically change how depression is treated. Furthermore, the likely higher remission rate with the combination may also reduce attrition during short-term and longer-term treatments for CRMD.

Such an approach, if effective and safe, and if associated with better longer-term outcomes, is of great public health significance. Antidepressant medication combinations may (1) reduce patient attrition, (2) have pharmacological additive effects or create a broader spectrum of action in short-term treatment, (3) have long-term benefits. There is also safety/tolerability and efficacy data from pilot and other studies supporting this treatment approach.

More vigorous first step pharmacological approaches could reduce patient attrition. The recently completed Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial provided longer than usual first treatment visits, and extra focus, attention, and education by the Clinical Research Coordinators (CRCs). Nevertheless, 8% of eligible participants left the study after only a baseline visit. Another 20.5% left escitalopram treatment without proceeding to either Level 2 or to follow-up after one or more postbaseline visits.[34] These retention rates are better than rates found in practice, but they are poor from a public health perspective. Most STAR*D participants had CRMD and, thus, were unlikely to fare well without treatment. If more participants received greater and/or more rapid benefit in the first step without a substantially greater side-effect burden, they, in theory, would be more likely to stay in treatment.

The combination of two antidepressants may produce additive pharmacological effects by affecting a broader range of neurotransmitters and/or by the creation of a broader spectrum of action (i.e., treating a broader range of patients) than can be achieved with monotherapy. Thus, two agents used together at the first treatment step should increase remission rates by (a) treating a broader range of patients, some of whom might remit with each agent alone, and (b) creating additive pharmacologic effects such that the second agent will increase the efficacy of the first agent.

The likelihood of additive pharmacological effects is suggested by evidence that at least three neurotransmitter systems (norepinephrine or NE, dopamine or DA, serotonin or 5HT) are involved in depression, based on both clinical and postmortem studies.[35] Evidence of the involvement of the serotonin system is clear from neuroendocrine studies,[35] Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) studies,[36-38] and postmortem studies.[39;40] The involvement of NE is supported by postmortem studies.[35;41] The role of DA neurotransmission in depression has been supported by brain imaging,[35] neuroendocrine, and postmortem studies.[42] Combination treatments are further justified by neuroimaging studies that reveal a heterogeneous neurobiology of depression,[43;44] which is consistent with the notion that some medications may help some patients, while others require another agent, and that some may uniquely respond/remit only to the combination.

Maintenance of response or remission may be improved with combination treatment. Clinically, relapse or symptom breakthrough is common following short-term response or remission with antidepressant monotherapy.[45] In practice, these patients often continue their current medication and a second medication is added. We have no randomized, controlled trial evidence by which to select among potential combination or augmentation agents to reverse relapse/recurrence. We also do not know whether combinations that are more effective in the short term will also be associated with more consistent, better longer-term symptom control. However, it is certainly logical to expect that more effective short-term treatments will also be more effective in the longer term.

Finally, there are safety/tolerability and efficacy data supporting both combinations. We have completed a pilot study of the BUP-SR + S-CIT combination, and have data on the MIRT+VEN-XR combination from STAR*D (Level 4) and from Blier et al.[46] In the pilot study of BUP-SR + S-CIT (Leuchter et al., submitted), we evaluated 51 outpatients with nonpsychotic CRMD recruited from five Depression Trials Network (DTN) Clinical Sites. Two-thirds of participants had chronic depression (index MDE > 2 years) and three-fourths were recurrent; 41% had no prior treatment, 39% had one, and 20% had $\geq$2 prior treatments. Dosing began at baseline with S-CIT 10 mg/day, and BUP-SR (150 mg/day) was added at week 1. Doses could be raised to 20 mg/day for S-CIT and 400 mg/day for BUP-SR. Final exit doses were 327($\pm$81) (BUP-SR) and 16 ($\pm$5) mg/day (S-CIT). No hypertension and minimal weight changes were found by exit. At exit, only one participant had an Abnormal Involuntary Movement Scale (AIMS) score of $\geq$2. Of 51 participants, 3 discontinued due to side effects (two of whom were in week 1). Five participants discontinued after only a baseline visit. The full intent-to-treat sample (i.e., including the 5 who discontinued after only a baseline visit) yielded a 50% remission rate and a 62% response rate. By exit, 64% of those with no prior treatments, 58% of those with one prior treatment, and 10% with $\geq$2 prior treatments were remitted. These study results suggest that this combination should yield far higher remission rates than expected with S-CIT monotherapy, and that the combination can be well dosed with acceptable tolerability.

In the Blier et al.[46] study four acute first step treatments were compared: placebo (PBO) + fluoxetine (FLUO) (n=28), FLUO + MIRT (n=25), MIRT + VEN-XR (n=26), and BUP-SR + MIRT (n=26) in depressed outpatients (initial $HRSD_{17}$=22). Remission rates were 25%, 52%, 58%, and 46%, respectively (all three combinations were statistically superior to PBO + FLUO). As compared to FLUO + PBO, the NNT for remission was 4, 3, and 5, respectively. Response rates were 54%, 64%, 73%, and 65% respectively. Dropout rates (all causes) were 18%, 16%, 12%, and 15%, respectively (not different). Thus, these combination treatments (and MIRT+VEN-XR specifically) seem to enhance acute remission rates without substantially

increasing side-effect burden. Evidence that these combinations are effective also comes from the relapse rates following discontinuation of one of the agents for patients who reached at least a (Montgomery Asberg Depression Rating Scale – [MADRS]) of 12 after 7-8 weeks of acute treatment.[46] Relapse rates were 6/16, 4/18, and 8/17 for FLUO + MIRT, MIRT + VEN-XR, and BUP-SR + MIRT, respectively. In an analysis of the STAR*D data, McGrath et al.[47] found patients in the VEN-XR + MIRT treatment cell tolerated the combination quite well. Further, patients in the comparison group, tranylcypromine, discontinued at a significantly higher rate due to intolerability than those treated with VEN-XR + MIRT.

The proposed study tests whether these different specific medication combinations used as first step treatment result in greater remission rates than monotherapy. We will compare a highly selective SSRI (S-CIT) against each of two different antidepressant medication combinations. The first is BUP-SR + S-CIT, which combines a highly selective SSRI with a NE and DA reuptake inhibitor, BUP-SR. The second combines VEN-XR (i.e., a NE + 5HT reuptake inhibitor) with MIRT (a 5HT NE reuptake inhibitor plus an alpha-2 adrenergic receptor antagonist).

In sum, the major public health impact of CRMD, the most common and disabling form of depression, is indisputable. In STAR*D, even after up to 28 weeks of treatment with two medication treatment steps, only half of the CRMD participants would have remitted had they stayed in treatment under enhanced care conditions. In fact, about 28% exited treatment within the first 14 weeks. If combination antidepressant medications are found to produce greater remission rates, retention rates, and/or were to have more sustained benefits than monotherapy, practice guidelines would be revised.

CONCISE PROJECT SUMMARY

In all, 660 adult participants with CRMD, between the ages of 18 and 75, will be enrolled at primary and specialty care sites across the USA. All participants will be randomly assigned (1:1:1 ratio) to receive a combination of escitalopram (S-CIT) plus placebo, bupropion SR (BUP-SR) plus S-CIT, or venlafaxine XR (VEN-XR) plus MIRT for up to 28 weeks of treatment.

Participants in the S-CIT and placebo treatment group will begin on S-CIT 10 mg/day and 1 placebo pill (at week 2) and will proceed through a dosing schedule to a maximum of 20 mg/day escitalopram, and two placebo pills per day. The S-CIT will be given open label, but the second medication will be given single blind (i.e. the participants will not know that the second medication is a placebo). Both medications will be taken orally. Participants in the BUP-SR and S-CIT treatment group will begin on BUP-SR 150 mg/day. At week 1 the BUP- SR will be increased to 300 mg/day. At week 2 S-CIT 10 mg/day (single blind) will be added. Participants will proceed through a dosing schedule to a maximum of 20 mg S-CIT and 400 mg BUP-SR with oral administration of both. The BUP-SR will be given open label, but participants will not know that the second medication is S-CIT. Participants in the VEN-XR and MIRT treatment group will begin on 37.5 mg of VEN-XR for 3 days, increasing to 75 mg/day at day 4 and 150 mg/day at week 1. MIRT will start at 15 mg/day (single blind) at week 2. The VEN-XR will be given open label, but the participants will not know that the second medication is MIRT. Participants will proceed through a dosing schedule to a maximum of 300 mg/day of VEN-XR, and 45 mg/day of MIRT, with both medications being orally administered. Participants will be told that there will be four medications and a placebo in this study, and they will receive either

one or two active medications, but they will not be told which combinations are being studied so they will not be able to infer the identity of the blinded medication in each pair.

Participants may learn of the possibility of participating from their treating physician or clinic staff or may be recruited by flyers and/or posters in the clinic. After written informed consent, study staff will perform a diagnostic interview and determine eligibility for participation (see inclusion and exclusion criteria). The diagnosis of MDD (nonpsychotic) will be made by the study investigators and confirmed with selected modules from the MINI International Neuropsychiatric Interview (M.I.N.I.). After the initial screen and baseline evaluation, participants will be seen in the clinic at weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, and 28 for assessment of medication tolerability, symptom severity (including suicidal ideation), and associated symptoms. The baseline visit will take 60-90 minutes and each follow-up visit 45-60 minutes.

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 Points-Dosing Tables (see Appendix II). Clinical management will be informed by the Quick Inventory of Depressive Symptomatology – Clinician-rated version (QIDS-C_{16}),[1;2] which evaluates depression symptom severity, and by the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER)[8] and the Systematic Assessment for Treatment Emergent Events – Systematic Inquiry (SAFTEE-SI),[10] the latter two providing information about medication tolerability.

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

DESCRIPTION OF THE DEPRESSION TRIALS NETWORK (DTN) FOR THIS STUDY

The DTN provides a trained and experienced platform and investigative teams with which to conduct studies of substantial public health importance in the treatment of depression in "real world" practice settings. This geographically diverse network has 15 Regional Centers (academic institutions) and 33 primary and specialty care Clinical Sites. The DTN provides the opportunity to enroll participants who are presenting for clinical care in studies rather than the symptomatic volunteers typically found in efficacy studies.

One primary or psychiatric care Clinical Site per Regional Center has been selected for CO-MED by the Regional Center Director in collaboration with the PI and the National Coordinating Center (NCC) study team. Site selection for CO-MED was based on sites' prior performance in STAR*D or prior DTN pilot studies in terms of recruitment and retention; racial, ethnic, and economic diversity in study population or geography; operational management skill in key leadership; and committed clinical support.

The study will be overseen by the DTN's National Coordinating Center (NCC) (The University of Texas Southwestern Medical Center) and assisted by the Data Coordinating Center (DCC) (Epidemiological Data Center at the University of Pittsburgh). Participants 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.

For this study, each Regional Center (RC) oversees work at its Clinical Site (CS), which will screen, recruit, and follow participants in the CO-MED protocol. Each CS will follow the same protocol, overseen by the RC and coordinated by the NCC. Each RC is responsible for arranging for training and ongoing support and supervision of the Clinical Research Coordinator (CRC) who implements the protocol at the CS. Each CS is responsible for the clinicians and clinical support staff.

Data management and analysis is coordinated through the Data Coordinating Center (DCC) in Pittsburgh (Stephen Wisniewski, PhD, PI). The DCC is accountable directly to the study PI.

Study monitoring, coordination, and monitoring of personnel are provided by the National Coordinating Center (NCC) in Dallas (A. John Rush, MD, PI). The NCC provides central coordination across all components of the study and ensures the delivery of optimal performance in the start-up and implementation phases of the protocol, and coordinates the publication and dissemination of study findings. In STAR*D, a Web-based clinical management flag system was developed to monitor medication dosing and side effects for each participant to ensure the consistent delivery of protocol-recommended treatment. The system was remarkably effective in identifying specific cases or clinicians needing intervention. It will be adapted to tablet PCs for treatment in CO-MED for site monitoring.

Four committees (Project Management Team, NCC Study Management Team, Operations Committee, and the Publications Committee) will oversee CO-MED. This infrastructure, developed and successfully used in STAR*D, is designed to maximize scientific integrity, participant safety, and effective and cost-efficient project execution.

The Project Management Team (PMT) oversees the study, ensures it achieves its aims, makes key policy decisions, and provides weekly project management. The PMT makes key operational determinations, monitors study progress toward specific goals, and devises and directs interventions to improve performance. The NCC Study Management Team oversees day-to-day study operations, financial management, and performance management. It intervenes to continuously improve performance as indicated. The Operations Committee oversees the development, implementation and day-to-day progress of data collection and transmission, oversees the site visit process, and intervenes to continuously improve performance as indicated. The Publications Committee delivers study findings, methods, and innovations in a timely, effective, and comprehensive manner. Committee membership is determined based on the specific expertise of the participants. Ongoing teleconferences for Regional Center and Clinical Site Directors and teleconferences for Clinical Research Coordinators address ongoing operational issues during study start-up and ongoing implementation.

NATIONAL COORDINATING CENTER

The NCC is responsible for the scientific and operational leadership of this multicenter, randomized clinical trial for participants with CRMD who present for care at the 15 representative primary care (PC) and specialty care (SC) Clinical Sites (CSs) across the country. The primary purpose of the NCC is to provide central coordination across all components of a large and geographically broad infrastructure and to execute the study in accordance with the protocol. The NCC ensures optimal performance in the start-up and implementation phases of

the protocol and coordinates the publication and dissemination of study findings. The specific aims of the NCC are:

To provide scientific leadership, direction, and oversight for the study. This aim is accomplished by developing the protocol for the study, providing overall scientific management and oversight of the execution of the clinical trial; maintaining scientific integrity; coordinating the implementation of the protocol with scientific investigators at the DCC and RCs; providing ongoing review for possible protocol changes; providing scientific oversight and input for the development, review, and approval of pharmacogenetic ancillary studies for submission to NIMH; and developing and participating in planning and writing manuscripts to ensure productivity and dissemination of scientific findings through high quality peer-reviewed publications.

To provide clinical oversight, training, and quality control to ensure rapid and scientifically rigorous implementation of the protocol. This aim is accomplished through finalizing assessment measures and clinical and data procedures; developing the Clinician and Clinical Research Coordinators (CRC) Procedures Manual and training procedures for Study Clinicians, Regional Center Directors (RCDs), Clinical Site Directors (CSDs), and CRCs; providing training and oversight of clinical and research study staff; providing quality control for clinical medication management and data management procedures, ensuring ongoing participant safety; and overseeing changes in study clinical procedures when indicated for scientific or safety issues.

To provide administrative oversight and management of the study to ensure successful implementation of the protocol. This is accomplished by maintaining contracts with RCs and CSs; collaborating with RCs to open and close CSs for the study; ensuring that study services meet the needs of a diverse participant population; coordinating communications, including arranging teleconferences, face-to-face meetings, and site visits; and maintaining communication logs of meetings, teleconferences, emails, and minutes of committee meetings. The NCC ensures that all required reports are submitted to NIMH and communications are maintained with the DCC and the Data Safety Management Board (DSMB). The NCC oversees approvals of the protocol and consent forms, RCs' and CSs' compliance with regulatory issues including maintaining current IRB forms, HIPAA authorizations, and ethics certifications (human subjects training) of study personnel as required.

To provide budget and fiscal management for the study. This aim is accomplished by providing oversight of the budget, payments to CSs for uninsured treatment visits, participant reimbursements, clinician payments, payments to vendors, as well as management of the NCC office.

DATA COORDINATING CENTER

The goals of the Data Coordinating Center (DCC) are to support the National Coordinating Center (NCC) in the scientific oversight of the trial; to facilitate the collaboration among the investigators; and to collect, manage and analyze all study data.

The specific aims of the DCC are to:

Provide Methods of Data Entry and Data Management: The DCC will implement a data entry and management system to ensure the highest quality data by developing checks for logical inconsistencies and reports to the NCC, Regional Centers, and Clinical Sites including: recruitment, retention, missing data, participant follow-up visit schedules, and treatment adherence.

Facilitate Procedures and Carry Out Quality Control: The DCC will design all data collection forms, prepare manuals of operations, train and certify all study personnel, conduct site visits, and develop systems to report serious adverse events to the appropriate organizations.

Assume Responsibility for Reporting, Statistical Design, and Analysis: The DCC will design and implement a system for random treatment assignment, develop regularly scheduled reports, including Data and Safety Monitoring Board (DSMB) reports, and conduct final and interim analyses.

Provide a Comprehensive Communication System and Administrative Support: The DCC will develop and maintain a comprehensive communication system, via the CO-MED Web site, arrange conference calls, draft and disseminate minutes to data analysis working group meetings and provide reimbursement reports.

REGIONAL CENTERS

The RC Directors (RCDs) directly manage the execution of CO-MED at affiliated CSs based on their knowledge of their communities and experience in the recruitment and retention of participants, including minority participants. The RCs span the entire country (13 states) to deliver a diverse participant pool in terms of geographic, racial, ethnic, and socioeconomic status to provide maximum generalizability of study findings.

RCDs are responsible for all aspects of the operations and performance of their respective RCs, and for implementation of the study protocol from both a scientific and operational standpoint at their CSs. They have a local presence and can identify and respond to local issues that can impact the trial (e.g., clinician changes, hospital closings). They oversee participant recruitment, retention, and safety; the acquisition of study data; delivery of protocol-defined treatment; and budgetary management. The RCDs hire, train, supervise, manage, and replace Clinical Research Coordinators (CRCs); identify and train "backup" CRCs for times when CRCs are unavailable; and meet with CRCs weekly to oversee clinical care, study procedures, and data quality.

The CRCs are vital to the implementation of the protocol and are responsible (along with the CS Study Clinicians) for the management of participants and the study protocol at each CS. The CRCs (located at each CS 4½ days per week) have a primary relationship with participants and Study Clinicians and are critical to successful recruitment and retention of participants. The CRCs gather and transmit clinical data. They collect intake and clinic visit information, manage participant data, and assist Study Clinicians in the timely reporting of Serious Adverse Events (SAEs).

The RCDs ensure local Institutional Review Board (IRB) approvals, human subjects training certifications, and ensure conformance to all regulatory requirements (e.g., ethics, HIPAA) for the RC and its CSs. They oversee that the CSs obtain IRB and other regulatory approvals (when applicable). The RCDs train the Study Clinicians in all protocol and operational requirements, with assistance from the CS Directors (CSDs) and PIs. Standardized training materials are developed by the NCC collaboratively with RCDs to ensure consistency and that all relevant information is readily available.

The RCDs are responsible for ensuring that each CS has sufficient numbers of adequately trained Study Clinicians available throughout the study and oversee that key performance targets are met at each CS. These targets include recruitment, retention, treatment fidelity, and clinical data collection. They see that all safety procedures are followed, and that required study data and reports are submitted to the DCC and/or NCC. The RCDs closely supervise the affiliated CSs,

and will develop and implement corrective actions should CS performance not meet standards and requirements. They also conduct regular weekly to monthly visits (as needed) to each CS to review/solve administrative or other obstacles to adequate performance. In collaboration with the NCC and under the direction of the Project Management Team they replace CSs in the event of unplanned events affecting a site's continuation in the study or nonperformance. They ensure the NCC is appropriately notified about participant, clinician, and treatment costs. RCDs will also participate in the publication and dissemination processes.

CLINICAL SITES

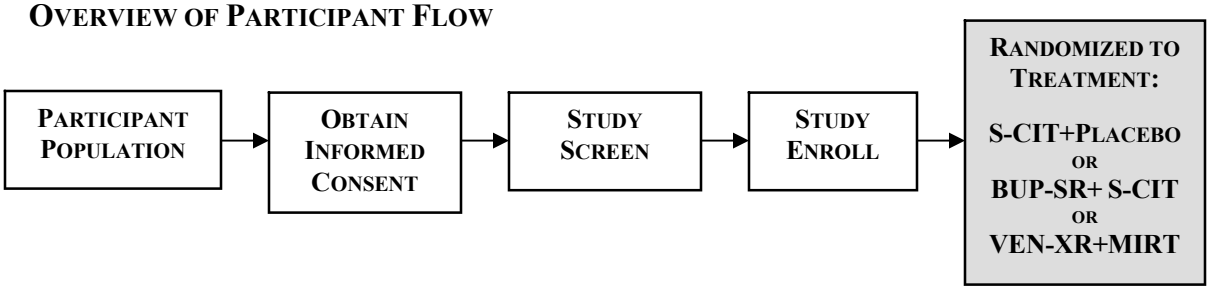
For CO-MED, each RC has one affiliated CS, including both primary and specialty psychiatric care settings in both the public and private sector to enhance generalizability of findings. Almost all of these CSs participated in STAR*D. The remaining DTN CSs will be "backup" Clinical Sites for CO-MED, should they be needed for any reason.

The CS has primary responsibility for identifying, recruiting, treating, and following eligible participants for the study as specified in the study protocol. The CSD assists the RCD in carrying out activities to ensure fidelity to the protocol and submission of required documents and high quality data to the DCC and/or NCC. The CSD is also responsible for Study Clinicians following safety procedures and meeting performance standards for treatment fidelity, recruitment, retention, outcome data collection, and other performance targets identified by the Project Management Team.

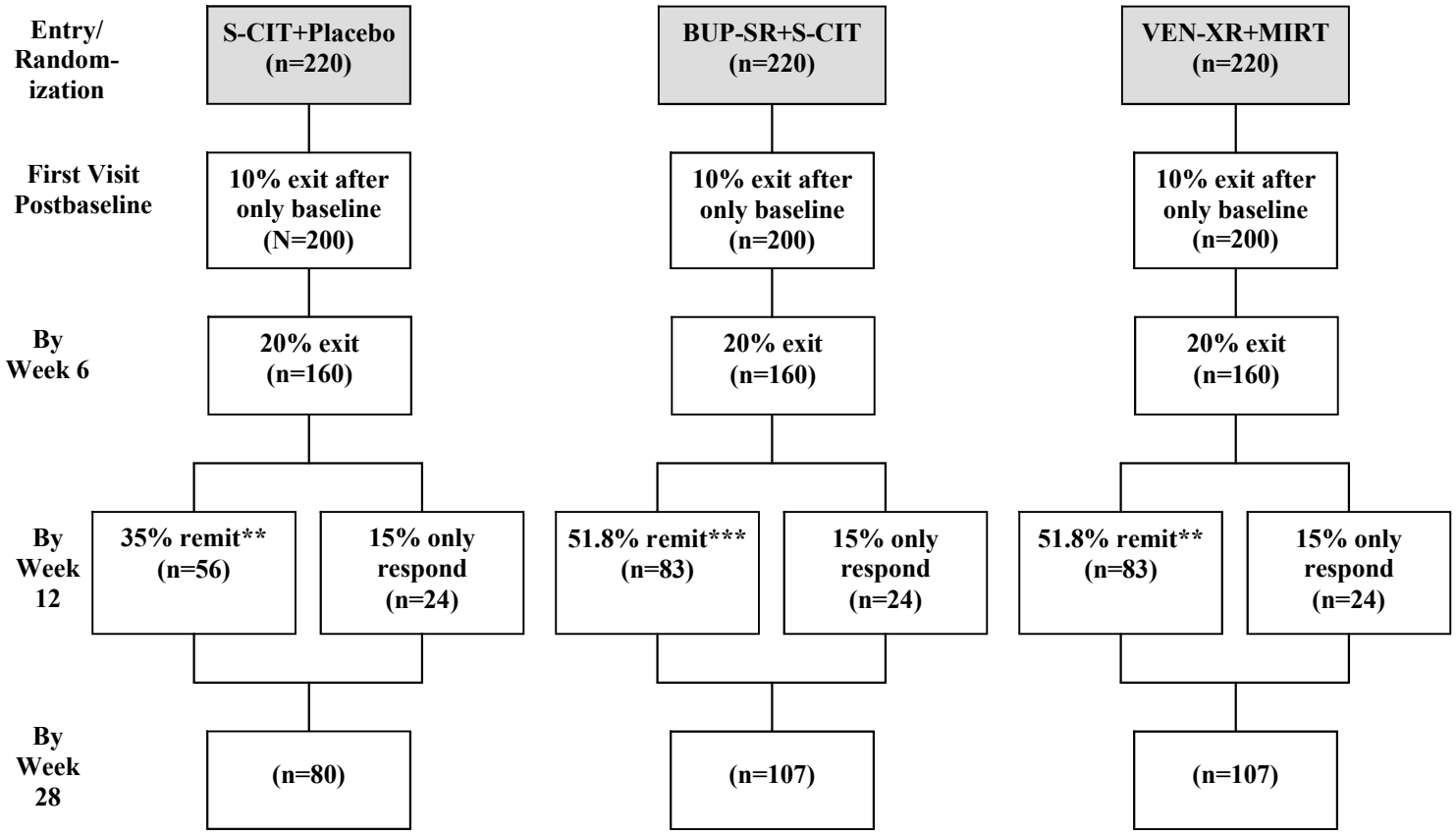
The CS will provide sufficient adequately trained Study Clinicians throughout the study to meet their performance targets and remain up-to-date with human subjects training and any other regulatory requirements.

SCHEMA

OVERVIEW OF PARTICIPANT FLOW



ESTIMATES OF PATIENT FLOW AT VARIOUS TIMES IN THE STUDY*



* Numbers beyond randomization are only estimates.

** Thus, the full Intent-To-Treat (ITT) sample expected remission rate is 56/220 = 25%.

*** Thus, based on the full ITT sample, the expected remission rates are at least 83/220 = 38% or greater at week 12.

ELIGIBILITY

CO-MED will enroll 660 participants (44 participants per Clinical Site) of both genders and all ethnic/racial and socioeconomic backgrounds. The inclusion criteria are broad and the exclusion criteria are few, such that participants with most comorbid general medical or psychiatric disorders are generally included to provide a broadly representative sample. Participants of all ethnic and racial groups and both genders are eligible. Special efforts will be made to recruit minority participants at all Clinical Sites. The broad inclusion and minimal exclusion criteria are designed to obtain a broadly representative participant population.

Clinical evaluation based on interview together with review of medical history form will be employed by study physicians to determine eligibility.

CRITERIA FOR INCLUSION OF SUBJECTS

- Patients must be seeking treatment at the primary or specialty care site, and be planning to continue living in the area of that clinic for the duration of the study
- Patients must be 18-75 years old
- Patients must meet clinical criteria for nonpsychotic MDD, recurrent (with the current episode being at least 2 months in duration), or chronic (current episode $\geq$ 2 years) as defined by a clinical interview and confirmed by the MINI International Neuropsychiatric Interview (M.I.N.I.).
- Screening $HRSD_{17}$ score ≥ 16
- Treatment with antidepressant medication combinations is clinically acceptable.
- Patients must give written informed consent
- Patients with and without current suicidal ideation may be included in the study as long as outpatient treatment is clinically appropriate

CRITERIA FOR EXCLUSION OF SUBJECTS

- Patients who are pregnant or breastfeeding
- Patients who plan to become pregnant over the ensuing 8 months following study entry or are sexually active and not using adequate contraception
- History (lifetime) of psychotic depression, schizophrenia, bipolar (I, II, or NOS), schizoaffective, or other Axis I psychotic disorders
- Current psychotic symptom(s)
- History (within the last 2 years) of anorexia or bulimia
- Current primary diagnosis of obsessive compulsive disorder
- Current substance dependence that requires inpatient detoxification or inpatient treatment
- Patients requiring immediate hospitalization for a psychiatric disorder
- Definite history of intolerance or allergy (lifetime) to any protocol medication

- History of clear nonresponse to an adequate trial of an FDA-approved monotherapy in the current MDE if recurrent, or during the last 2 years if chronic (see Appendix IV for the definition of an adequate trial)
- History of clear nonresponse to an adequate trial of escitalopram or S-CIT, BUP-SR, VEN-XR, or MIRT (see Appendix IV for the definition of an adequate trial) used as a monotherapy, or to one or more of the protocol combinations in the current or any prior MDE
- Patients currently taking any of the study medications at any dose
- Patient having taken Prozac (fluoxetine) or an MAOI in the prior 4 weeks
- Patients with an unstable general medical condition (GMC) that will likely require hospitalization or to be deemed terminal (life expectancy < 6 months after study entry)
- Patients who are taking medications or have GMCs that contraindicate any study medications (e.g., seizure disorder)
- Patients requiring medications for their GMCs that contraindicate any study medication
- Epilepsy or other conditions requiring an anticonvulsant
- Lifetime history of having a seizure including febrile or withdrawal seizures
- Patients who are receiving or have received (lifetime) vagus nerve stimulation (VNS), electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), or other somatic antidepressant treatments
- Patients currently taking or having taken within the prior 7 days, any of the following exclusionary medications: antipsychotic medications, anticonvulsant medications (gabapentin, pregabalin, and topiramate are allowed for pain as determined by the treating clinician), mood stabilizers, or central nervous system stimulants.
- Antidepressant medication used for the treatment of depression or other purposes such as smoking cessation or pain are excluded since these agents may interfere with the testing of the major hypotheses under study (low dose trazodone is allowed for insomnia, $\leq$ 200 mg/day).
- Uncontrolled narrow angle glaucoma
- Patients taking thyroid medication for hypothyroidism may be included only if they have been stable on the medication for 3 months
- Patients using agents within the prior 7 days that are potential augmenting agents (e.g., T_3 in the absence of thyroid disease, SAMe, St. John's Wort, lithium, buspirone)
- Depression-focused psychotherapy including Cognitive Therapy (CT), Interpersonal Psychotherapy of Depression (IPT), Cognitive Behavioral Assessment System of Psychotherapy (CBASP), Problem-Solving Therapy, and light therapy will not be allowed during participation. Patients can participate if they are receiving psychotherapy that is not targeting the symptoms of depression, such as individual therapy, group therapy, family or couples therapy.

DESCRIPTION OF AGENT

Escitalopram, manufactured by Forest Pharmaceuticals under the name Lexapro, is a selective serotonin reuptake inhibitor (SSRI) that is FDA approved for use in oral administration for the treatment of MDD. The efficacy of Lexapro in MDD was established in three, 8-week placebo controlled trials in outpatients whose diagnosis corresponded most closely to the DSM-IV category of MDD. The recommended dosing of Lexapro is 10 mg per day in single dosing, but effectiveness was shown in 20 mg per day dosing.

Bupropion SR, manufactured by GlaxoSmithKline under the name Wellbutrin SR, is a relatively weak inhibitor of the neuronal uptake of serotonin, norepinephrine, and dopamine and is unrelated to other known antidepressant medications. It is also FDA approved for the treatment of MDD. Wellbutrin was initially marketed in the immediate release tablet and is now available in the sustained release (SR), as well as an extended release (XL) form. Dosing is recommended to begin at 150 mg, to be taken in the morning, and can be increased to 400 mg per day if no response is seen in the lower doses, with higher dosages being split so no single dose exceeds 200 mg. Wellbutrin is contraindicated with patients who have a seizure disorder and with patients who have anorexia nervosa or bulimia nervosa because of a higher incidence of seizures noted in patients with bulimia who were treated with the immediate release Wellbutrin.

Venlafaxine HCL, manufactured by Wyeth Pharmaceuticals under the name Effexor and provided in the extended release formulation Effexor XR, is a serotonin-norepinephrine reuptake inhibitor that is FDA approved for the treatment of MDD. Recommended dosing is 75 mg per day, increasing to 350-375 mg per day for more severely depressed inpatients.

Mirtazapine, manufactured by Organon Inc. under the name Remeron, is an orally administered tetracyclic antidepressant available in 15 mg, 30 mg, and 45 mg tablets. Mirtazapine enhances central noradrenergic and serotonergic activity, and is approved by the FDA for the treatment of MDD. The recommended dosage of mirtazapine for patients with MDD ranges from 15 mg to 45 mg per day.

The comparative efficacy and tolerability of these medications in combination for the treatment of MDD, while common in practice, has not been established. None of these combinations has received FDA approval, although the individual medications are approved by the FDA for use alone.

SOURCES OF RESEARCH MATERIAL

At the initial visit, the Clinical Research Coordinator (CRC) ensures that participants understand the purpose of the study, the risks and benefits of study participation, and obtains written informed consent. From there, the CRC completes the screening assessments and reviews the inclusion/exclusion criteria for eligibility. The CRC will present the information to the study clinician for confirmation of the clinical diagnosis of MDD and agreement that all eligibility diagnostic criteria are met. If study eligible, baseline measures are obtained. Outcome assessments, collected at baseline and subsequent visits, measure: 1) symptoms, 2) functional status/quality of life, 3) side effects, and 4) treatment adherence.

Research materials include clinical, demographic, and family history information. Clinical information obtained includes medical and psychiatric treatment history, symptom assessment, as well as level of functioning and quality of life assessments. Collection of family history includes psychiatric disorders and suicide in first degree relatives. Participants' medical records

will also be reviewed. Information will be collected by CRCs and study clinicians and will include both participant interviews and self-report questionnaires. Interviews include the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$)[48;49] to assess depressive features; the 30-item Inventory of Depressive Symptomatology - Clinician version ($IDS\text{-}C_{30}$)[2-4] to assess for atypical, melancholic, and anxiety features; and the Clinical and Demographics Data Form (CDDF). The $QIDS\text{-}C_{16}$ is embedded in the $IDS\text{-}C_{30;}$ therefore, the $QIDS\text{-}C_{16}$ total score will be derived from the $QIDS\text{-}C_{16}$ items that are contained in the $IDS\text{-}C_{30.}$ Medication compliance will be tracked using a two-question medication Adherence Questionnaire (AQ), study medications will be recorded on the CRF (Case Report Form), and concomitant medications will be tracked on the Concomitant Medications Tracking form (CMT). Self-reports include the 16-item Quick Inventory of Depressive Symptomatology - Self-report ($QIDS\text{-}SR_{16}$),[1;2] the FIBSER,[8] and SAFTEE-SI[9;10] to assess global and specific side effects as well as the burden of these symptoms; the Self-Administered Comorbidity Questionnaire (SCQ)[50] to assess GMCs; the Work Productivity and Activity Impairment Scale (WPAI),[5] Work and Social Adjustment Scale (WSAS),[6] and the Quality of life Inventory (QOLI)[51-53] to assess day-to-day function and quality of life; the Psychiatric Diagnostic Screening Questionnaire (PDSQ)[54;55] to evaluate for concurrent Axis I disorders; and the Cognitive and Physical Functioning Questionnaire (CPFQ)[56] to assess cognitive and physical well-being. Additionally, the Suicidality Rating Scale (SRS), Suicidality Rating Scale - Associated Symptoms (SRS-AS), and the Altman Self-Rating Mania Scale (ASRM)[57] will be used to identify treatment-emergent morbid thoughts, mania, or psychosis. We may obtain blood samples for genetic studies through a separate protocol if approved by NIMH. The consent form will ask participants to allow us to reconsent them for future studies.

Whenever participants exit the study, study exit forms are completed. If the participant does not return for a final visit, the CRC contacts the participant to complete all ratings and the study exit forms whenever possible.

ELECTRONIC DATA CAPTURE

A growing body of literature shows the acceptance and reliability of electronic data collection systems. These systems have been shown to be accepted by both patients and clinicians,[58;59] preferred by patients over paper-and-pencil data collection,[60] and reliable.[61] The process of collecting data using an electronic data system can require more time of the clinician during the data collection phase, but in the long run, time savings are realized since reduced time for auditing of the data more than makes up for the up-front time investment.[58;62]

A Tablet PC data entry system will be used as the first step in the Electronic Data Capture (EDC). Data collection/entry on the Tablet PC will be done by the participant in the waiting room or exam room, as well as by the CRC or treating physician (e.g., during the exam). Laptops will be secured to furniture in the office by a small locking cable.

All Tablet PCs will also be loaded with current study operating procedure manuals, which will be updated electronically as needed, and data transfer software. Each Tablet PC will be equipped with a docking station for battery recharging and connection to the Internet.

Communication with the DCC to enable data transfers will be established through the Internet. Because the Tablet PC will be attached to its docking station overnight, an automated process built into the Table PC software will be implemented to password protect the data file and transfer it over the Internet using SSL and 128-bit encryption to a secure File Transfer Protocol (FTP) server at the DCC which restricts connections by Internet Protocol (IP) address.

Each participant will be identified by a unique study identification number. Each sender will have a unique username and password embedded in the code of the transfer to enable unattended data transfers. Once the file has been transferred successfully, the Tablet PC's transfer routine will add transfer confirmation to a master file stored in the central database as well as on the Tablet PC.

Upon arrival at the DCC, the data will be loaded into a SQL Server database, which will be updated with each regularly scheduled transfer. Quality control programs and standard data management reports will be implemented to ensure that the data are complete and accurate. Data will be stored at the DCC on a secure sever in a SQL Server database.

CLINICAL, DEMOGRAPHIC, AND PRIOR TREATMENT HISTORY

Clinical/Demographic Data Form (CDDF): The CDDF records age, gender, education, total monthly income, ethnic/race (self-declared), medical history (including menstrual history for women), psychiatric history (primary Obsessive Compulsive Disorder, Anorexia Nervosa, or Bulimia Nervosa in the last 2 years; possible past abuse or trauma), and past treatment history.

CLINICAL MEASURES OF PSYCHIATRIC COMORBIDITY

MINI International Neuropsychiatric Interview (M.I.N.I.): The M.I.N.I. diagnostic interview includes items that assess the hallmark symptoms of the exclusionary Axis I disorders: psychotic depression, schizophrenic, bipolar (I, II, or NOS), schizoaffective, or other Axis I psychotic disorders (lifetime). We will use the MDD, Bipolar, and Psychosis modules only.

Psychiatric Diagnostic Screening Questionnaire (PDSQ): The PDSQ is a patient self-report assessment consisting of 125 yes-or-no items. 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.

Suicidality Rating Scale (SRS): This scale may be administered either by a clinician or as a patient self report assessment. The scale consists of 12 items rated on a fully anchored 5-point Likert scale with responses ranging from 1 (strongly disagree) to 5 (strongly agree). The patient is asked to rate items ranging in severity from mild ("I feel as if things are never going to get better"), to moderate ("I feel that there is no reason to live"), to severe (i.e. "I have been having thoughts of killing myself" and "I have a plan to kill myself"). The scale yields a total score ranging from 12 to 60.

Suicidality Rating Scale - Associated Symptoms (SRS-AS): This scale in the self-report format consists of 17 items rated on a fully anchored 5-point Likert scale with responses ranging from 1 (strongly disagree) to 5 (strongly agree). Items assess symptoms of anxiety, tension, irritability, impulsivity, psychomotor agitation, physiologic hyperarousal, and hypomania/mania. The scale yields a total score ranging from 17 to 85.

Altman Self-Rating Mania Scale (ASRM): The ASRM is a 5-item, patient self-rating mania scale, designed to assess the presence and/or severity of manic symptoms occurring during the last week. All items are scored from 0 (absent) to 4 (present to a severe degree), based on increasing severity. Total scores may range from 0 to 20.

Cognitive and Physical Functioning Questionnaire (CPFQ): The CPFQ is a 7-item patient self-report assessment of cognitive and physical well-being. Each item is rated on a 6–point, fully anchored Likert scale with responses ranging from 1 (greater than normal), 2 (normal), to 6 (totally absent).

MEASURES OF DEPRESSIVE SEVERITY

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.

Inventory of Depressive Symptomatology - Clinician rated ($IDS\text{-}C_{30}$): This clinician-rated, 30-item measure assesses the 9 DSM symptom criteria for a major depressive episode, as well as symptoms of melancholic, atypical and anxious depression.

Quick Inventory of Depressive Symptomatology – Self-Report ($QIDS\text{-}SR_{16}$): This 16-item patient self-report measure 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 measurement-based care of several prior trials.

MEASURES OF QUALITY OF LIFE

The Quality of Life Inventory (QOLI): The QOLI is a 32-item comprehensive self-report of satisfaction in 16 areas of life, such as love, work, and health. Each area is rated in terms of satisfaction and the relationship of that area to overall quality of life. It yields an overall raw score and satisfaction ratings for the 16 individual areas of life. The QOLI raw score is an average of weighted satisfaction ratings computed only over areas of life judged to be Important or Extremely Important to the respondent.

The Work Productivity and Activity Impairment scale (WPAI): The WPAI is a 6-item self-report used in STAR*D, measures total work hours missed, hours missed due to depression, loss of work productivity because of depression while at work, and impact of disease on regular (nonemployment) related work activities. These scores are sensitive to change in depressive symptoms. The WPAI provides a specific measure of work performance (e.g., missed days, inefficient work performance), which facilitates calculation of economic costs.

The Work and Social Adjustment Scale (WSAS): The WSAS is a 5-item self-report scale, assessing the patient's view of ability to work, to manage affairs at home and socially, and to form and maintain close relationships. Each question is rated on a 0 to 8 Likert scale (0 indicating no impairment at all; 8 indicating very severe impairment) (range: 0-40). A WSAS score above 20 suggests at least moderately severe functional impairment.

MEASURES OF MEDICATION SIDE EFFECTS

Frequency, Intensity, and Burden of 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): This is an easy-to–use, 55-item self-report with items rated none, mild, moderate, or severe. It also rates global side-effect burden. The items include most commonly reported side effects with new(er) antidepressant medications. This measure will be used to descriptively compare short- and longer-term side effects associated with protocol treatment.

MEASURES OF MEDICAL COMORBIDITIES

Self-administered Comorbidity Questionnaire (SCQ): The SCQ is a 40 item self-report, which assesses the presence of medical problems, their severity, and whether or not the condition limits functioning. The medical conditions specified on the SCQ include: heart disease, high blood pressure, lung disease, diabetes, ulcer or stomach disease, kidney disease, liver disease, anemia or other blood disease, cancer, depression, arthritis, thyroid disease, and back pain. Respondents have the option of adding three additional conditions. An individual can receive a maximum of 3 points for each medical condition (1 point for its presence, 1 point if they receive treatment for the condition, and 1 point if the condition limits activities).

MEASURE OF ADHERENCE

Adherence Questionnaire (AQ): The 2-item AQ will be used to determine if the patient took each medication as recommended, and to establish the reason(s) for deviating from the recommended dose (e.g., forgot, side effects, thought to not be needed, etc.).

MEDICATIONS

Study medication tracking form (RX): The RX form will be used to track study medications.

Concomitant Medications Tracking form (CMT): The CMT will be used to track concomitant medications.

LAB TESTS

Vital signs will be recorded at each visit (height, weight, blood pressure, pulse rate). No laboratory tests are required for this protocol. Clinicians can conduct relevant laboratory tests at any point in the study to determine pregnancy status and to manage concomitant GMCs. A separate protocol and consent will be added to collect blood for genetic or metabolomic studies.

Copies of study instruments are in Appendix V.

Data will be entered into the database by the use of participant 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.

Table 1: SCHEDULE OF ASSESSMENTS

		WEEK												
INSTRUMENT	**(RATER)**	**SCREEN**	**BL**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**28**
EL	(CRC)	•												
M.I.N.I.*	(CRC)	•												
CDDF	(CRC)	•												
$HRSD_{17}$	(CRC)	•												
CMT	(CRC)		•	•	•	•	•	•	•	•	•	•	•	•
RX	(CRC)		•	•	•	•	•	•	•	•	•	•	•	•
VS	(CRC)		•	•	•	•	•	•	•	•	•	•	•	•
$IDS\text{-}C_{30}$[a]	(CRC)		•	•	•	•	•	•	•	•	•	•	•	•
SCQ	(P)		•											
PDSQ	(P)		•											
CPFQ	(P)		•	•	•	•	•	•	•	•	•	•	•	•
SRS	(P)		•	•	•	•	•	•	•	•	•	•	•	•
$QIDS\text{-}SR_{16}$	(P)		•	•	•	•	•	•	•	•	•	•	•	•
SAFTEE-SI	(P)		•	•	•	•	•	•	•	•	•	•	•	•
FIBSER	(P)			•	•	•	•	•	•	•	•	•	•	•
AQ	(P)			•	•	•	•	•	•	•	•	•	•	•
ASRM	(P)		•	•	•	•	•	•	•	•	•	•	•	•
WPAI	(P)		•	•	•	•	•	•	•	•	•	•	•	•
WSAS	(P)		•	•	•	•	•	•	•	•	•	•	•	•
QOLI	(P)		•	•	•	•	•	•	•	•	•	•	•	•
SRS-AS	(P)		•	•	•	•	•	•	•	•	•	•	•	•

AQ = Adherence Questionnaire
ASRM = Altman Self-Rating Mania Scale
CDDF = Clinical and Demographic Data Form
CPFQ = Cognitive and Physical Functioning Questionnaire
CMT = Concomitant Medication Tracking form
EL = Eligibility Form
FIBSER = Frequency, Intensity, and Burden of Side Effects Rating
$HRSD_{17}$ = 17-item Hamilton Rating Scale for Depression
$IDS\text{-}C_{30}$ = 30-item Inventory of Depressive Symptomatology – Clinician-rated
MINI = MINI International Neuropsychiatric Interview
PDSQ = Psychiatric Diagnostic Screening Questionnaire
RX = Study medication tracking form
$QIDS\text{-}SR_{16}$ = 16-item Quick Inventory of Depressive Symptomatology - Self-report
QOLI = Quality of Life Inventory
SAFTEE-SI = Systematic Assessment for Treatment Emergent Events - Systematic Inquiry
SCQ = Self-Administered Comorbidity Questionnaire
SRS = Suicidality Rating Scale
SRS-AS = Suicidality Rating Scale – Associated Symptoms
VS = Vital Signs (BP, P, weight)
WPAI = The Work Productivity and Activity Impairment scale
WSAS = Work and Social Adjustment Scale

BL = baseline
CRC = Clinical Research Coordinator
P = Patient

[a] $IDS\text{-}C_{30}$ provides $QIDS\text{-}C_{16}$ total score to guide medication management and measures key associated symptoms
*MDD, Bipolar, and Psychosis modules

POWER ANALYSIS

Each combination (BUP-SR + S-CIT, MIRT+VEN-XR) will be compared to the monotherapy (S-CIT). To control for the overall type I error rate, a type I error rate of .025 will be used and will maintain an overall type I error rate of .05. Sample size calculations are based on a one-sided alternative hypothesis, 80% power, a type I error rate of 2.5% for each comparison, and an estimated baseline rate of remission in the S-CIT group of 25% in the short-term study. With an estimated remission rate of 25% in the S-CIT group and a sample size of 220 per group, there will be 80% power to detect an increase in remission rates of 12.8% or greater. It is expected that the overall remission rate in the S-CIT arm will be lower in the longer term, so smaller increases will be able to be detected. For example, if the remission rate is 15% in the S-CIT arm of the longer-term study, there will be 80% power to detect an increase in remission rates of 11.2% or greater. This assumes one observation per participant. As there will be more than one observation per person and the analytic approach employs a mixed-model that utilizes all observations, the size of the effect that can be detected will be smaller. The size of reduction is unknown and depends on the number of observations for each participant and the within-participant correlation (intraclass correlation) of the remission rates over time, which are unknown at this time.

RECRUITMENT OF PARTICIPANTS

Potential participants will be screened at each Clinical Site (CS) using the site's standard procedure (which may vary across sites). All CSs, however, will use the study standard inclusion/exclusion criteria for enrollment. Primary Care clinics in particular may screen for depression when participants register for their scheduled clinic appointments. Screening may include 2-9 questions from the 9-item Patient Health Questionnaire PHQ[63-65] or other methods if already in place locally. No participants will be excluded on the basis of race or ethnicity. All participants will provide written informed consent before study participation. Clinicians may also identify depressive symptoms in a patient who refuses the screen or does not score positively. CRCs will not approach these patients a second time unless the physician refers the patient to the study again at a later date. Should treatment be indicated, the clinician will review options with the patient, including possible participation in CO-MED. If a patient is willing to consider study participation, the Clinical Research Coordinator (CRC) will be informed and will see the patient while he or she is still in the clinic whenever feasible. The CRC will describe the study to the patient and offer the informed consent for their review. The CRCs are trained in how to obtain informed consent. The Institutional Review Boards (IRBs) at the NCC (University of Texas Southwestern Medical Center at Dallas), each participating Regional Center (RC), and the University of Pittsburgh DCC will approve the study protocol and all consent and study procedures. In addition, if needed, IRBs at all relevant CSs will approve the study protocol and all study procedures. Each RC will provide a specific recruitment plan for NCC approval prior to study initiation. The recruitment strategies employed by each RC will be customized to take into account the clinic flow, characteristics of the patient population seen, and the culture of each Clinical Site. The RC Director, CRC, and CS Director will meet weekly to monitor recruitment at the sites and modify strategies as needed to meet enrollment goals.

Whenever possible, the CRC will complete the screening procedures during the same clinic visit. If rescheduling of the screening/baseline visit is necessary due to time constraints, the CRC

and clinician will make all efforts to accommodate as consistent with good clinical care and study protocol.

In addition to the presence of the CRC in the clinic and the use of a depression screening tool, IRB-approved recruitment flyers and posters will also be developed according to IRB guidelines for display in the clinic waiting areas and exam rooms. These will raise awareness of the availability of CO-MED as a potential resource for care and will encourage patient self-referral. Participant referrals from clinics other than the CO-MED Clinical Site will be accepted as long as the person has presented for care and the Clinical Site can accept the person for care. No advertising will be used. The RC Director will also educate the clinic support staff and participating physicians about the study on an ongoing basis throughout the recruitment phase, providing updates of study progress to keep clinician interest high.

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

TREATMENT

CO-MED will enroll 660 representative depressed outpatients in both primary (PC) and specialty (SC) care practices in both the public and private sectors at 15 Clinical Sites (CSs). Adults (18-75 years of age) (both genders and all racial/ethnic groups) will be included. Broad inclusion and minimal exclusion criteria (as in STAR*D) will ensure a representative sample,[66;67] but we will include only participants with CRMD. All patients will meet DSM-IV TR[11] criteria for nonpsychotic MDD that is either recurrent (i.e., $\geq$ 1 prior major depressive episode or MDE) or chronic (i.e., in the current MDE for $\geq$ 2 years) as defined by Clinical Research Coordinator (CRC) patient interview. The diagnostic criteria for eligibility will be established clinically, and with the M.I.N.I.[68;69] Final determination for eligibility will be made by the study clinician.

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

MEDICATION BLINDING

CO-MED is designed as a single blind (participant only), placebo-controlled trial. The first medication given in each treatment cell will be open label (both participant and study personnel are unblinded). The second medication given in each treatment cell is blinded (participant only). In the escitalopram (S-CIT) + placebo treatment, the placebo medication is blinded; in the bupropion SR (BUP-SR) + S-CIT treatment cell, S-CIT is blinded; in the venlafaxine XR (VEN-XR) + MIRT treatment cell, MIRT is blinded. The blinded medications will be encapsulated (blinded) when distributed to sites. Participants will remain blind to the second study medication during both the short-term and the longer-term phases of the study; however, to maximize safety and the ability of physicians to make flexible dosing decisions, both the CRC and physician will not be blinded.

In the event of an emergency where the blind needs to be broken, the CRC will inform the medical or psychiatric team treating the emergency what study medication the participant is taking. If the study participant becomes aware of the study medication that had been masked, a protocol deviation will be recorded and the participant can remain in the study.

This study will compare the three medication treatments in terms of remission rates (QIDS-SR_{16}) after up to 12 weeks of treatment and at study end (28 weeks). Participants will be randomized (1:1:1 ratio) to S-CIT plus placebo (S-CIT) (n=220), BUP-SR plus S-CIT (n=220), or VEN-XR + MIRT (n=220). Treatment will be guided by clinician-rated symptom measures (the QIDS-C_{16}) and global side-effect measures (FIBSER) obtained at each treatment visit. Treatment visits will occur at baseline and at weeks 1, 2, 4, 6, 8, 10, and 12 and then monthly to ensure delivery of appropriate and yet vigorous and tolerable pharmacotherapy. Those with unacceptable or intolerable side effects that cannot be resolved with dose reduction or other strategies may elect to exit the study. Participants will remain in the study as long as clinician and participant view the benefit as sufficient and tolerable. Other participants will exit the study and be treated as clinically indicated.

The frequency of treatment visits for the short term is higher than typical practice and slightly higher than used in STAR*D, although the visit frequency is consistent with guidelines[70] and our experience with STAR*D. We chose a higher frequency because (a) seven post baseline visits are needed to safely yet appropriately titrate the combination treatments and (b) more frequent treatment visits should reduce attrition.[71] Clinicians may substitute a telephone visit for a face-to-face visit on up to three occasions if participants are doing well and it is clinically acceptable.

S-CIT + PLACEBO. S-CIT will begin at 10 mg/day. At week 2 a placebo pill will be added to the participant's daily medication. The 10 mg/day dose will be increased to 20 mg/day at 4 weeks if the QIDS-C_{16} is >5 (side effects allowing) and a second placebo pill will be added.

BUP-SR + S-CIT. BUP-SR is used up to a maximal dose of 400 mg/day. BUP-SR will be started at 150 mg/day at baseline and increased to 300 mg/day at week 1. At week 2, 10 mg/day of S-CIT will be added. Starting at week 4, S-CIT dosing may be raised to 20 mg/day, and BUP-SR may be raised to 400 mg/day if the QIDS-C_{16} is >5. Doses of BUP-SR of 300 mg/day should be taken as 150 mg twice a day, and doses of 400 mg/day should be taken as 200 mg twice a day. No single dosage should exceed 200 mg.

VEN-XR + MIRT. VEN-XR will begin at 37.5 mg/day for 3 days and then raised to 75 mg/day. At week 1, VEN-XR will be raised to 150 mg/day. At week 2, MIRT will be added (15 mg/day). At week 4, if QIDS-C_{16} is >5, VEN-XR will be raised to 225 mg/day and/or MIRT will be raised to 30 mg/day. At week 6, if QIDS-C_{16} >5, MIRT will be raised from 30 mg/day to 45 mg/day (maximum dose) and at week 8, VEN-XR will be raised from 225 mg/day to 300 mg/day (maximum dose) if QIDS-C_{16} >5.

See Appendix II Dosing Tables for a detailed description of the medication algorithms.

Clinical visits with CRC support will continue throughout the 28-week study using measurement-based care (MBC). If participants miss a monthly clinic visit, CRCs will complete these ratings by telephone. Additional treatment visits may occur based on clinical need and if they are held, the FIBSER and QIDS-C_{16} will be used to guide treatment. Typically, doses used at weeks 12-16 will continue throughout the study, but clinicians may raise (or lower) doses due to lack of remission defined at the clinic visits (QIDS-C_{16} >5) or due to the development/persistence of unacceptable side effects.

For the S-CIT plus placebo combination cell, either S-CIT or placebo will be increased if symptoms indicate a need (see Appendix II for dosing guidelines), and a return visit will be scheduled within 2 weeks following the dose increase. If the dosing table suggests increasing one or both medications, the clinician may increase both medications simultaneously, or can

increase only one of the combination medications. If increasing only one of the combination medications, the clinician is advised to first consider increasing the dosage of the primary medication (S-CIT), and to consider increasing the secondary medication in the combination (placebo) as a second choice.

For the BUP-SR plus S-CIT combination cell, either BUP-SR or S-CIT will be increased if symptoms indicate a need (see Appendix II for dosing guidelines), and a return visit will be scheduled within 2 weeks following the dose increase. If the dosing table suggests increasing one or both medications, the clinician may increase both medications simultaneously, or can increase only one of the combination medications. If increasing only one of the combination medications, the clinician is advised to first consider increasing the dosage of the primary medication (BUP-SR), and to consider increasing the secondary medication in the combination (S-CIT) as a second choice.

If an increase is needed for the VEN-XR + MIRT cell in the longer-term study, either MIRT or VEN-XR will be increased if clinically indicated (see Appendix II for dosing guidelines). A follow-up treatment visit will be scheduled within the first 2 weeks following any dose increase or decrease to monitor progress. The VEN-XR dose will be increased if the MIRT dose increase does not lead to QIDS-C ≤5 after week 4 following the initial MIRT dose increase. The maximal doses are 300 mg/day VEN-XR and 45 mg/day MIRT. If the dosing table suggests increasing one or both medications, the clinician may increase both medications simultaneously, or can increase only one of the combination medications. If increasing only one of the combination medications, the clinician is advised to first consider increasing the dosage of the primary medication (VEN-XR), and to consider increasing the secondary medication in the combination (MIRT) as a second choice.

Some medications have a higher risk of unwanted symptoms if the medication is stopped abruptly. Participants will be cautioned not to stop their medications abruptly during or after the study. Physicians are advised to use caution and down titrate all medication dosages slowly.

Patients having a less than 30% reduction in symptoms, as measured by the QIDS-C at weeks 8 and 10, may be considered for early study exit due to lack of treatment efficacy.

EXPECTED PARTICIPANT FLOW (see Figure 1)

Expected short-term remission and response rates are based on our STAR*D experience and pilot data. For each treatment cell (S-CIT; BUP-SR + S-CIT; VEN-XR + MIRT), we expect 220 to enter and 200 to return for at least one post baseline visit. Of these 200, we expect 20% (n=40) in each cell to exit by week 12 before completion based on our STAR*D experience. Of the remaining 160 participants on S-CIT, we expect 35% (n=56) to remit and another 15% (n=24) to respond. For each combination cell, we expect that at least 51.8% (n=83) will remit and another 15% (n=24) will respond. We expect roughly 80 participants to remain in the study after week 12 on S-CIT, and 107 in each combination cell.

EVALUATION CRITERIA

- The presence of MDD will be evaluated using the M.I.N.I and clinical interview.
- Clinical and demographic information will be documented on the CDDF.
- Baseline severity and study eligibility will be determined using the $HRSD_{17}$.

- Depressive symptom severity will be evaluated using the QIDS-SR_{16}, and IDS-C_{30}.
- Suicidal ideation and associated features will be assessed using the SRS and SRS-AS.
- Cognitive and physical well-being will be assessed using the CPFQ.
- Mania and psychosis will be measured using the ASRM.
- Day-to-day function and quality of life will be evaluated using the WPAI, WSAS, and QOLI.
- Medication side effects and tolerability will be assessed using the FIBSER and SAFTEE-SI.
- Psychiatric comorbidities will be identified using the PDSQ and clinical interview.
- Medical comorbidities will be identified using the SCQ and clinical interview.
- Medication adherence will be tracked using the AQ.
- Study medications will be tracked using the RX.
- Nonstudy medications will be tracked using the CMT.

STUDY TERMINATION CRITERIA

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

1. Physician Discretion: Participant deemed a potential danger to self or others.
2. Participant Choice: Participants 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 participant. However, some participants will choose to discontinue participation.
3. Participant Lost to Follow-up: If a participant has missed visits and the CRC is unable to contact the participant, the participant is considered "Lost to Follow-up".
4. Noncompliance: If a participant misses more than 2 weeks of both of the study medications, the participant cannot continue in 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 participant will need to be exited from the study.
6. Patients who are hospitalized for worsening of depression and/or suicidal ideation since hospitalization is likely to lead to treatment changes.

POTENTIAL RISKS

While there are risks of suffering from depression, the risks involved in this study do not exceed the risks associated with this combination in clinical practice. The primary risk of major depressive disorder is attempting or completing suicide. The principal risk of treatment is that nonresponders may be kept on these medication combinations longer than might be optimal.

Occasionally some discomfort may occur while filling out questionnaires or being interviewed about matters pertaining to mood, functioning, and other experiences. Completion of clinician rated assessments is basically hazard-free, with the possible exception that

confidentiality could be breached. Those referred for a medical exam, which will be based on clinician judgment, may experience mild discomfort during blood drawing for laboratory tests.

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. Recently, the FDA issued a warning that patients taking antidepressants be closely monitored for suicidal thinking and/or behavior. Although the FDA clearly states that there is no clear link between the use of these antidepressants and an increase in suicidal thinking or behavior, the warning has been issued to ensure that patients are adequately monitored for such changes. For this reason we are including a specific measure (SRS) to assess suicidality at each visit.

Human subject risk is minimal to modest since medications under study have FDA approval. The treatment durations in both the short- and longer-term studies are consistent with guideline recommendations. While the combinations of medications under study are used in practice, neither combination (MIRT+VEN-XR; BUP-SR + S-CIT) has FDA approval for the treatment of depression. In CO-MED, two different combinations are used, which may increase somewhat the risk of side effects as compared to simple monotherapies. Clinicians are not masked to medication type or dose so that appropriate dose adjustments can be made in a timely fashion. Furthermore, dose adjustments are guided by specific assessment of the magnitude and types of side effects at each clinic visit, and downward titration (as well as slower upward titrations) is allowed based on tolerability and efficacy. Therefore, the risks are minimally greater than usual clinical care.

Commonly observed side effects associated with the study medications 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.[72]

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%).

BUPROPION SR

Information about known problems is based upon the experiences of 490 men and women with MDD who have participated in past research using bupropion SR.[72]

In past research, 6 to 26% of people had these problems: headache (26%), dry mouth (24%), weight loss (19%), nausea (18%), insomnia (16%), dizziness (11%), sore throat (11%), constipation (10%), infection (9%), abdominal pain (9%), agitation (9%), diarrhea (7%), palpitations (6%), ringing in the ears (6%), muscle stiffness (6%), nervousness (6%), anxiety (6%), sweating (6%).

2 to 5% of people had these problems: increased urinary frequency (5%), increased sleep (5%), rash (5%), anorexia/reduced appetite (5%), vomiting (4%), itching (4%), joint stiffness (4%), feelings of weakness (4%), face flushing (4%), migraine (4%), change in taste (4%), hot flashes (3%), weight gain (3%), irritability (3%), chest pain (3%), decreased memory (3%), pain

(3%), problems with vision (3%), nasal congestion (3%), fever (2%), difficulty swallowing (2%), arthritis (2%), twitching (2%), nervous system stimulation (2%), tingling feeling (2%), increased cough (2%), hives (2%), increased urinary urgency (2%), vaginal hemorrhage (2%).

Bupropion SR has been associated with a risk of seizures (convulsions) of approximately 1 in 1000 patients. Therefore, it is contraindicated for individuals with known seizure disorder or people at high risk for seizures including those with eating disorders such as bulimia nervosa and anorexia nervosa.

VENLAFAXINE XR

Information about known problems is based upon the experiences of 357 men and women with MDD who have participated in past research using venlafaxine.[72]

In past research, 6 to 31% of people had these problems: nausea (31%), dizziness (20%), increased sleep (17%), insomnia (17%), sexual dysfunction (16%), increased sweating (14%), dry mouth (12%), nervousness (10%), feelings of weakness (8%), constipation (8%), anorexia (8%), abnormal dreams (7%), sore throat (7%).

2 to 5% of people had these problems: tremor (5%), flushing (4%), hypertension/high blood pressure (4%), vomiting (4%), increased gas (4%), abnormal vision (4%), weight loss (3%), depression (3%), tingling feeling (3%), decreased sex drive (3%), agitation (3%), increased yawning (3%).

Patients who quickly stop or quickly lower the dose of venlafaxine sometimes have new symptoms. Symptoms may include agitation, loss of appetite, anxiety, confusion, impaired coordination, diarrhea, dizziness, dry mouth, sad mood, muscle twitching, fatigue, headaches, sleeping too much, difficulty sleeping, upset stomach, nervousness, nightmares, sweating, tremor, dizziness, and vomiting. Adverse reactions have been reported in patients who have recently stopped taking an monoamine oxidase inhibitor (MAOI) and started on venlafaxine, or who have recently had stopped venlafaxine therapy before starting an MAOI. These symptoms may included tremor, muscle twitching, sweating, nausea, vomiting, flushing, dizziness, and convulsions.[72]

MIRTAZAPINE

Information about known problems is based upon the experiences of 453 men and women with MDD who have participated in past research using mirtazapine.[72]

In past research, 6 to 54% of people had these problems: increased sleep (54%), dry mouth (25%), increased appetite (17%), constipation (13%), increased weight (12%), muscle weakness (8%), dizziness (7%).

2 to 5% of people had these problems: flu syndrome (5%), peripheral edema/swelling (2%), abnormal dreams (4%), abnormal thinking (3%), tremor (2%), confusion (2%), urinary frequency (2%), muscle pain (2%).

In a premarketing clinical trials, 2 out of 2,796 patients treated with mirtazapine developed agranulocytosis (abnormally low levels of a specific type of white blood cells - granulocytes), and a third developed severe neutropenia (abnormally low levels of neutrophils - a specific type of white blood cell). All three patients recovered when mirtazapine was discontinued.

SPECIAL PRECAUTIONS AND STUDY MONITORING

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 participant contacts based on their selected clinic's specific crisis management requirements. All Regional Centers' risk management procedures will be reviewed and approved by the Project Management Team, which includes the Principal Investigator and the scientific and operational leadership of CO-MED.

Risk management procedures typically include the following: Participants 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 participant is in the clinic, the physician will be immediately notified to further assess the participant. If the participant is deemed an acute risk for suicide, the physician will direct the measures necessary to get the participant to safety, using clinic specific crisis management procedures. If the CRC identifies that the participant may be at acute risk during a phone assessment, a complete evaluation of the situation is necessary. For example, if the participant indicates thoughts of suicide/death several times a day in depth on the QIDS-C_{16}, the CRC will obtain information about the participant's intent, plan, and means at hand for suicide, as well as determine, as appropriate, the location of the participant and whether anyone else is with the person. Measures to keep the participant 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 participant responses to study instruments as well as in depth questioning of participants about current suicidality in either setting. Training will include case scenarios. There will be ongoing opportunities to discuss safety-related procedures and individual participant cases in semimonthly 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 participant s to minimize the risk of suicide. When necessary, hospitalization is available. Physician, CRC, and Investigator phone numbers are provided, and participant s are

encouraged to call should they need additional assistance beyond scheduled appointments. The clinicians and CRCs maintain close contact with participants and reschedule appointments as needed. Either the participant or the physician may discontinue the participant's study participation at any time should the participant's symptoms worsen or if the participant simply desires to withdraw. Use of these procedures minimizes risk.

At each visit, the participant 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 participant reports. Depression symptoms will be monitored at each visit, with the risk for suicide thoroughly assessed. All data forms completed by the participant will be reviewed for content by the CRC before the participant 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 participant 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 NIMH 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 participant enrollment. It will determine if study procedures should be altered or stopped because of evidence of benefit or harm to trial participants 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 participant confidentiality. CRCs will enter data by coded participant identification numbers, and records will be kept in locked filing cabinets at Regional Centers/Clinical Sites. No participants will be identified by name in publications. Any information that is obtained in connection with research that can be identified with a participant will remain confidential and can be disclosed only with a participant'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.

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.

A comprehensive security policy will govern all areas of the network. Several layers of security will be implemented. Tablet PCs will be shipped to the Clinical Sites with *authentication* activated and required when the Tablet PC is activated (i.e., turned-on), for access to the operating system, and entry into the data management software. Unique username and password combinations will be maintained and distributed by the DCC. Passwords will be changed at routine intervals to ensure access to the network is granted to only those intended. Screen saver passwords will be activated to protect the network and the privacy of participant data in the event personnel walk away from the computer equipment while logged in to the system.

In addition, the Tablet PCs have various software applications that will help ensure the secure operation of the devices. *Firewall* software will restrict communication to traffic that is absolutely critical for conducting this research. *Anti-virus* software will guard against the intrusions and installations that typically attack through malicious email and removable media. *Privacy protection and malware detection* software will be active in real-time as additional assurance that unwanted cookies, browser plug-ins, are not slowing performance of the device.

Additional security (e.g., *stateful inspection,* etc.) is provided from a router that will be installed and attached to each Clinical Site's Internet connection. This will prevent unwanted direct access to any devices (i.e., the Tablet PC) connected to the router. All CRCs will be instructed that the Tablet PCs are to be used for CO-MED only. All data communication between the CRCs and the DCC will either be encrypted via a VPN client necessary to access DCC network resources, or it will be protected using standard encryption methods on the open network (e.g., 128 bit Secure Socket Layer (SSL) over Hypertext Text Transfer Protocol Secure (HTTPS)).

For the DCC, a strict security policy is also enforced that includes elements such as IP filtering, authentication methods, encryption methods, and a firewall system to protect the data systems and databases from common network threats. The firewall provides the additional barrier between the Internet community and the DCC network resources. Regularly scheduled backups and archives at the DCC will protect central and local information from hard disk failures. Permanent archives of critical files will be stored in a secured off-site facility to prevent data loss due to catastrophic events.

Participant 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, when direct payment to the participant is sent from the NCC. 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

RANDOM TREATMENT ASSIGNMENT

Eligible and consenting participants will be randomly assigned to one of the three short-term treatments: 220 to S-CIT + placebo, 220 to BUP-SR + S-CIT, and 220 to VEN-XR + MIRT. A complete random assignment design will be implemented, where the participant and clinician must be in equipoise with all three possible treatment strategies. Random treatment assignment will be stratified by Clinical Site and random block sizes of three and six will be used to ensure balance, while minimizing the probability of identifying the next treatment assignment.

Random treatment assignment for the short-term study will occur using a Web-based randomization system. This system has been successfully implemented by the Data Coordinating Center in several trials, including the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD).[73-75] For the short-term treatment study, the CRC obtains consent and completes a brief on-line form on a protected area of the CO-MED Web site, after which the randomly assigned treatment is provided to the CRC within seconds.

BASELINE DATA ANALYSES

The data analyses for the primary short-term and longer-term study aims will begin by describing the sociodemographic, psychiatric, and medical characteristics of the population at baseline. Descriptive statistics, including measures of central tendency and dispersion will be computed for continuous data such as age. Frequency distributions will be estimated for categorical data such as sex. To assure a balanced random treatment assignment, we will examine the treatment assignments in relationship to demographic, psychiatric and medical characteristic using the appropriate parametric (e.g., t-test) or nonparametric test (e.g., chi-square, Wilcoxon tests).

PRIMARY OUTCOME ANALYSES

All primary outcome analyses will be conducted based on the Intention-to-Treat (ITT) principle.

SPECIFIC AIM 1

To compare the short-term (12-week) outcomes of escitalopram (S-CIT) with those of bupropion SR plus S-CIT (BUP-SR + S-CIT), and with those of venlafaxine-XR plus mirtazapine (VEN-XR + MIRT) based on symptom remission rates defined by the 16-item Quick Inventory of Depressive Symptomatology – Self-report ($QIDS\text{-}SR_{16}$).[1;2]

Each combination (BUP-SR + S-CIT, VEN-XR + MIRT) will be compared to the monotherapy (S-CIT + placebo). To control for the overall type I error rate, a type I error rate of .025 will be used. The analytic approach for the two comparisons (BUP-SR + S-CIT vs. S-CIT + placebo and VEN-XR + MIRT vs. S-CIT + placebo) will be identical. A chi-square test will be used to compare the remission rates across the treatment groups. Remission will be defined as a score of a total score of $\leq$5 on one and $\leq$7 of the over of the last two $QIDS\text{-}SR_{16}$ assessments. To control for possible site effects, a logistic regression model will be used, including main effect for treatment and Clinical Site. The inclusion of a treatment-by-Clinical Site interaction will be investigated. However, given the large number of Clinical Sites (15), it may not be possible to estimate this interaction term.

SPECIFIC AIM 2

To compare the short-term (12-week) outcomes of these three treatments in terms of other symptoms (e.g., anxiety as assessed by the 30-item Inventory of Depressive Symptomatology – Clinician-rated (IDS-C_{30});[2-4] function as assessed by the Work and Productivity Inventory (WPAI),[5] Work and Social Adjustment Scale (WSAS),[6] and Quality Of Life Inventory (QOLI);[7] cognitive and physical well-being evaluated with the Cognitive and Physical Functioning Questionnaire (CPFQ); suicidality and associated psychiatric symptoms assessed with the Suicidality Rating Scale (SRS) and the Suicidality Rating Scale - Associated Symptoms (SRS-AS); side-effect burden as measured by the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER);[8] specific side effects as gauged by the Systematic Assessment for Treatment Emergent Events-Systematic Inquiry (SAFTEE-SI);[9;10] and attrition.

As was done for Specific Aim 1, analyses will be conducted separately for the comparison of each combination therapy to monotherapy. For dimensional variables, such as the measures of function, analysis of variance techniques will be used to compare the means across the treatment groups. For discrete variables, such as attrition due to side effects, chi-square tests will be used to compare the rates across the treatment groups. To control for possible site effects, a linear, logistic and ordinal logistic (for ordinal discrete variables with more than two levels, such as maximum side-effect burden) regression model will be used, including main effects for treatment and Clinical Site. The inclusion of a treatment-by-Clinical Site interaction will be investigated. However, given the large number of Clinical Sites (15), it may not be possible to estimate this interaction term.

SECONDARY AIM 1

To compare the three treatments in terms of longer-term, sustained effects (up to 28 weeks) in terms of depressive symptoms (QIDS-SR_{16}).

As was done in the analysis of the short-term outcome, each combination (BUP-SR + S-CIT, VEN-XR + MIRT) will be compared to the monotherapy (S-CIT). To control for the overall type I error rate, a type I error rate of .025 will be used. The analytic approach for the two comparisons (BUP-SR + S-CIT vs. S-CIT + placebo and VEN-XR + MIRT vs. S-CIT + placebo) will be identical.

Unlike the first aim where remission was defined as sustained remission (requiring two consecutive visits), remission for this aim will be defined as a QIDS-$SR_{16} \leq 5$. This definition will be used because the frequency of the visits (monthly) after week 12 do not occur with sufficient frequency two consecutive visits that are close in time to assess sustained remission. Under intention to treat, those who do not achieve remission an choose to exit the study at any time will be assumed to not be in remission for the entire period of the longer-term phase.

Mixed-effect ordinal logistic regression models will be used to compare the long-term outcome of the treatments. As stated earlier, remission status (presence/absence) will be collected based on the QIDS-SR_{16}. The model will contain main fixed-effects for treatment time and Clinical Site. The differential effect of treatment by Clinical Site and over time will be

investigated by including Clinical Site-by-treatment and time-by-treatment interactions in the ordinal mixed-effect models. The models will also include random effects for intercept and slope.

In addition, a similar analysis will be conducted examining the total severity of depression measured by the QIDS-SR_{16}. In this instance, a mixed-effect regression model will be used instead of the mixed-effect ordinal logistic regression model.

SECONDARY AIM 2

To compare the three treatment approaches in terms of long-term effects, including symptoms such as anxiety, function, quality of life, cognitive and physical well-being, suicidality and associated psychiatric symptoms, specific side effects and side-effect burden, and attrition.

The analytic approach for Secondary Aim 2 will be identical to the approach taken for Secondary Aim 1.

EXPLORATORY ANALYSES

SECONDARY AIM 3

What are the potential mediators and moderators of the short- and longer-term outcomes?

Exploratory analyses will be conducted to identify potential mediators and moderators of the short- and longer-term outcomes.

Exploratory analyses will be undertaken to identify possible moderators of response to the treatments.[76] Characteristics examined will include, among others, age, race, and ethnicity. Moderators are defined as baseline variables that define subgroups of the population where one treatment might work better than another. Mediators are defined as variables that are measured after the random assignment of treatment. The identification of moderators and mediators will be done using logistic regression models and Recursive Partitioning Methods.

ANCILLARY ANALYSES

During the course of a trial, a number of ancillary analyses are identified. These include analyses of the baseline characteristics of the population (e.g., do those with anxious depression have different baseline characteristics than those without anxious depression), psychometric analyses, and analyses of tertiary outcomes (e.g., factors associated with increases in suicidal ideation). The CO-MED investigators have been very productive in publishing reports of ancillary data analyses for STAR*D, with 88 papers published or in press and more than 50 additional topics identified for future analyses.

As was done in STAR*D, the DCC will be responsible for working with the CO-MED investigators to identify ancillary analysis topics, design and conduct the appropriate data analyses, and draft and edit manuscripts for publication in the scientific literature. Dr. Wisniewski and the lead data analyst for the project will meet with the lead author and Drs. Rush and Trivedi from the NCC via teleconference to review the shells of the tables to be included in the scientific report as derived from the questions and design of the analyses. After the call, the table shells will be modified and the lead data analyst will conduct the statistical analyses. Upon completion of the analyses, a second conference call with the lead author, the NCC team, and all

co-authors will be conducted to review the analyses, assign writing tasks, and identify additional analyses that will need to be conducted.

This procedure requires a significant amount of communication among the lead analyst and the lead author. All communication and deadlines will be tracked through the CO-MED Publications and Presentations Monitoring System (see DCC application).

POTENTIAL BENEFITS

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

Participants will (a) receive study protocol medication at no cost; (b) have more frequent treatment visits than is typical in practice; (c) be diligently followed in terms of symptoms and side effects at each treatment visit; (d) receive treatment at no cost if there is no insurance or other third-party coverage (those with insurance must provide the co-pay costs); (e) receive treatment at no cost if insurance runs out; (f) receive education about depression and its management; (g) receive compensation for each extended assessment visit: $40 for the baseline visit, $70 after at least 4 weeks in the study if the study exit forms have been completed, and $20 each for the week 16, 20, 24, and 28 visits; and (h) receive the extra time, attention, and interaction with the CRC at treatment visits and via telephone as needed between visits.

RISK BENEFIT ASSESSMENT

The potential benefit is the discovery of a more effective treatment approach for depressed patients. Participants will also receive free evaluation, monitoring and treatment and medications for their depression. Risks to participants are reasonable in relation to the anticipated benefits to the participants and in relation to the importance of the knowledge that may result.

REFERENCES

1. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry 2003;54: 573-583. Erratum p. 585.

2. Trivedi MH, Rush AJ, Ibrahim HM, Carmody TJ, Biggs MM, Suppes T, Crismon ML, Shores-Wilson K, Toprac MG, Dennehy EB, Witte B, Kashner TM. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. Psychol Med 2004;34: 73-82

3. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med 1996;26: 477-486

4. Rush AJ, Carmody TJ, Reimitz PE. The Inventory of Depressive Symptomatology (IDS): clinician (IDS-C) and self-report (IDS-SR) ratings of depressive symptoms. Int J Methods Psychiatr Res 2000;9: 45-59

5. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4: 353-365

6. Mundt JC, Marks IM, Shear MK, Greist JH. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. Br J Psychiatry 2002;180: 461-464

7. Endicott J, Nee J, Harrison W, Blumenthal R. Quality of Life Enjoyment and Statisfaction Questionnaire: A new measure. Psychopharmacol Bull 1993;29: 321-326

8. Wisniewski SR, Rush AJ, Balasubramani GK, Trivedi MH, Nierenberg AA. Self-rated global measure of the frequency, intensity, and burden of side effects. J Psychiatr Pract 2006;12: 71-79

9. Levine J, Schooler NR. General versus specific inquiry with SAFTEE. J Clin Psychopharmacol 1992;12: 448

10. Levine J, Schooler NR. SAFTEE: a technique for the systematic assessment of side effects in clinical trials. Psychopharmacol Bull 1986;22: 343-381

11. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed, Text Revision. Washington DC: American Psychiatric Press; 2000

12. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003;289: 3095-3105

13. Dawson R, Lavori PW, Coryell WH, Endicott J, Keller MB. Maintenance strategies for unipolar depression: an observational study of levels of treatment and recurrence. J Affect Disord 1998;49: 31-44

14. Depression Guideline Panel. Clinical Practice Guideline, Number 5: Depression in Primary Care, Volume 1: Detection and Diagnosis. U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No. 93-0550. 1993

15. Akiskal HS, Akiskal K. Cyclothymic, hyperthymic and depressive temperaments as subaffective variant of mood disorders. In: Tasman A, ed. American Psychiatric Press Review of Psychiatry 11 ed. Washington, DC: American Psychiatric Press, Inc.; 1992:43-62

16. Kocsis JH, Klein DN. Diagnosis and Treatment of Chronic Depression. New York: Guilford Press; 1995

17. Schulberg HC, Katon W, Simon GE, Rush AJ. Treating major depression in primary care practice: an update of the Agency for Health Care Policy and Research Practice Guidelines. Arch Gen Psychiatry 1998;55: 1121-1127

18. Birmaher B, Ryan ND, Williamson DE, Brent DA, Kaufman J, Dahl RE, Perel J, Nelson B. Childhood and adolescent depression: a review of the past 10 years. Part I. J Am Acad Child Adolesc Psychiatry 1996;35: 1427-1439

19. Klein DN, Schwartz JE, Rose S, Leader JB. Five-year course and outcome of dysthymic disorder: A prospective, naturalistic follow-up study. Am J Psychiatry 2000;157: 931-939

20. Keller MB, Klein DN, Hirschfeld RMA, Kocsis JH, McCullough JP, Miller I, First MB, Holzer CP, III, Keitner GI, Marin DB, Shea T. Results of the DSM-IV mood disorders field trial. Am J Psychiatry 1995;152: 843-849

21. Keller MB, Shapiro RW. "Double depression": superimposition of acute depressive episodes on chronic depressive disorders. Am J Psychiatry 1982;139: 438-442

22. Cornwall PL, Scott J. Partial remission in depressive disorders. Acta Psychiatr Scand 1997;95: 265-271

23. Klein DN, Schatzberg AF, McCullough JP, Dowling F, Goodman D, Howland RH, Markowitz JC, Smith C, Thase ME, Rush AJ, LaVange L, Harrison WM, Keller MB. Age of onset in chronic major depression: relation to demographic and clinical variables, family history, and treatment response. J Affect Disord 1999;55: 149-157

24. Wittchen HU, Pittrow D. Prevalence, recognition and management of depression in primary care in Germany: the Depression 2000 study. Hum Psychopharmacol 2002;17 Suppl 1: S1-11

25. Keller MB, Lavori PW, Endicott J, Coryell W, Klerman GL. "Double depression": two-year follow-up. Am J Psychiatry 1983;140: 689-694

26. Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. J Affect Disord 1993;29: 85-96

27. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51: 8-19

28. Weissman MM, Leaf PJ, Bruce ML, Florio L. The epidemiology of dysthymia in five communities: rates, risks, comorbidity, and treatment. Am J Psychiatry 1988;145: 815-819

29. McCullough JP, Jr., Klein DN, Keller MB, Holzer CE, Davis SM, Kornstein SG, Howland RH, Thase ME, Harrison WM. Comparison of DSM-III-R chronic major depression and major depression superimposed on dysthymic disorder (double depression): Validity of the distinction. J Abnorm Psychol 2000;109: 419-427

30. Keller MB, Gelenberg AJ, Hirschfeld RM, Rush AJ, Thase ME, Kocsis JH, Markowitz JC, Fawcett JA, Koran LM, Klein DN, Russell JM, Kornstein SG, McCullough JP, Davis SM, Harrison WM. The treatment of chronic depression, part 2: a double-blind, randomized trial of sertraline and imipramine. J Clin Psychiatry 1998;59: 598-607

31. Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ, Markowitz JC, Nemeroff CB, Russell JM, Thase ME, Trivedi MH, Zajecka J. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med 2000;342: 1462-1470

32. Koran LM, Gelenberg AJ, Kornstein SG, Howland RH, Friedman RA, DeBattista C, Klein D, Kocsis JH, Schatzberg AF, Thase ME, Rush AJ, Hirschfeld RM, LaVange LM, Keller MB. Sertraline versus imipramine to prevent relapse in chronic depression. J Affect Disord 2001;65: 27-36

33. Thase ME, Rush AJ, Howland RH, Kornstein SG, Kocsis JH, Gelenberg AJ, Schatzberg AF, Koran LM, Keller MB, Russell JM, Hirschfeld RM, LaVange LM, Klein DN, Fawcett J, Harrison W. Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. Arch Gen Psychiatry 2002;59: 233-239

34. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M. Evaluation of outcomes with escitalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006;163: 28-40

35. Fava M, Kendler KS. Major depressive disorder. Neuron 2000;28: 335-341

36. Siever LJ, Buchsbaum MS, New AS, Spiegel-Cohen J, Wei T, Hazlett EA, Sevin E, Nunn M, Mitropoulou V. d,l-fenfluramine response in impulsive personality disorder assessed with [18F]fluorodeoxyglucose positron emission tomography. Neuropsychopharmacology 1999;20: 413-423

37. Malison RT, Price LH, Berman R, van Dyck CH, Pelton GH, Carpenter L, Sanacora G, Owens MJ, Nemeroff CB, Rajeevan N, Baldwin RM, Seibyl JP, Innis RB, Charney DS. Reduced brain serotonin transporter availability in major depression as measured by [123I]-2 beta-carbomethoxy-3 beta-(4-iodophenyl)tropane and single photon emission computed tomography. Biol Psychiatry 1998;44: 1090-1098

38. Sargent PA, Kjaer KH, Bench CJ, Rabiner EA, Messa C, Meyer J, Gunn RN, Grasby PM, Cowen PJ. Brain serotonin1A receptor binding measured by positron emission tomography with [11C]WAY-100635: effects of depression and antidepressant treatment. Arch Gen Psychiatry 2000;57: 174-180

39. Owens MJ, Nemeroff CB. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. Clin Chem 1994;40: 288-295

40. Stockmeier CA, Shapiro LA, Dilley GE, Kolli TN, Friedman L, Rajkowska G. Increase in serotonin-1A autoreceptors in the midbrain of suicide victims with major depression-postmortem evidence for decreased serotonin activity. J Neurosci 1998;18: 7394-7401

41. Klimek V, Stockmeier C, Overholser J, Meltzer HY, Kalka S, Dilley G, Ordway GA. Reduced levels of norepinephrine transporters in the locus coeruleus in major depression. J Neurosci 1997;17: 8451-8458

42. Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. Neuron 2002;34: 13-25

43. Kalia M. Neurobiological basis of depression: An update. Metabolism 2005;54: 24-27

44. Rogers MA, Kasai K, Koji M, Fukuda R, Iwanami A, Nakagome K, Fukuda M, Kato N. Executive and prefrontal dysfunction in unipolar depression: a review of neuropsychological and imaging evidence. Neurosci Res 2004;50: 1-11

45. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163: 1905-1917

46. Blier P, Tremblay PM, Ward HE, Herbert C, Bergeron R. Antidepressant drug combination from treatment initiation to improve therapeutic response to major depression. Poster presented at the 18th European College of Neuropsychopharmacology Congress, October 22-26.
Amsterdam, The Netherlands: 2005

47. McGrath PJ, Stewart JW, Fava M, Trivedi MH, Wisniewski SR, Nierenberg AA, Thase ME, Davis L, Biggs MM, Shores-Wilson K, Luther JF, Niederehe G, Warden D, Rush AJ. Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR*D report. Am J Psychiatry 2006;163: 1531-1541

48. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23: 56-62

49. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6: 278-296

50. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis Rheum 2003;49: 156-163

51. Frisch MB. Manual and Treatment Guide for the Quality of Life Inventory. Minneapolis, MN: National Computer Systems, Inc.; 1994

52. Frisch MB, Clark MP, Rouse SV, Rudd MD, Paweleck JK, Greenstone A, Kopplin DA. Predictive and treatment validity of life satisfaction and the quality of life inventory. Assessment 2005;12: 66-78

53. Lehman AF. A quality of life interview for the chronically mentally ill. Eval Program Plann 1988;11: 51-62

54. Zimmerman M, Mattia JI. A self-report scale to help make psychiatric diagnoses: the Psychiatric Diagnostic Screening Questionnaire. Arch Gen Psychiatry 2001;58: 787-794

55. Zimmerman M, Mattia JI. The Psychiatric Diagnostic Screening Questionnaire: development, reliability and validity. Compr Psychiatry 2001;42: 175-189

56. Fava M, Graves LM, Benazzi F, Scalia MJ, Iosifescu DV, Alpert JE, Papakostas GI. A cross-sectional study of the prevalence of cognitive and physical symptoms during long-term antidepressant treatment. J Clin Psychiatry 2006;67: 1754-1759

57. Altman EG, Hedeker D, Peterson JL, Davis JM. The Altman Self-Rating Mania Scale. Biol Psychiatry 1997;42: 948-955

58. Beinlich I, Bokemeyer C, Rath U, Walter-Kirst R, Hartlapp J, Muschiol J, Fraass U, Schneider HT. Pen-based remote data entry system. A pilot clinical trial. Arzneimittelforschung 1993;43: 399-404

59. Bousquet J, Wouters F, van Cauwenberge P, Lund V, El Akkad T. Electronic patient diary is well accepted by patients and investigators in recording daily data in seasonal allergic rhinitis trials. Allergy 2000;55: 194-195

60. Berthelsen CL, Stilley KR. Automated personal health inventory for dentistry: a pilot study. J Am Dent Assoc 2000;131: 59-66

61. McBride JS, Anderson RT, Bahnson JL. Using a hand-held computer to collect data in an orthopedic outpatient clinic: a randomized trial of two survey methods. Med Care 1999;37: 647-651

62. Tiplady B, Jamieson A, Crompton G. Use of pen-based electronic diaries in an international clinical trial of asthma. Drug Inf J 2000;34: 129-136

63. Kroenke K, Spitzer RL, Williams JB. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. Psychosom Med 2002;64: 258-266

64. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. Med Care 2003;41: 1284-1292

65. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. Validity of a brief depression severity measure. J Gen Intern Med 2001;16: 606-613

66. Fava M, Rush AJ, Trivedi MH, Nierenberg AA, Thase ME, Sackeim HA, Quitkin FM, Wisniewski S, Lavori PW, Rosenbaum JF, Kupfer DJ. Background and rationale for the sequenced treatment alternatives to relieve depression (STAR*D) study. Psychiatr Clin North Am 2003;26: 457-494, x

67. Rush AJ, Fava M, Wisniewski SR, Lavori PW, Trivedi MH, Sackeim HA, Thase ME, Nierenberg AA, Quitkin FM, Kashner TM, Kupfer DJ, Rosenbaum JF, Alpert J, Stewart JW, McGrath PJ, Biggs MM, Shores-Wilson K, Lebowitz BD, Ritz L, Niederehe G. Sequenced Treatment Alternatives to Relieve Depression (STAR*D): rationale and design. Control Clin Trials 2004;25: 119-142

68. Pinninti NR, Madison H, Musser E, Rissmiller D. MINI International Neuropsychiatric Schedule: clinical utility and patient acceptance. Eur Psychiatry 2003;18: 361-364

69. Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Janavs J, Weiller E, Bonara LI, Keskiner A, Schinka J, Knapp E, Sheehan MF, Dunbar GC. Reliability and validity of the MINI International Neuropsychiatric Interview (M.I.N.I.): According to the SCID-P. Eur Psychiatry 1997;12: 232-241

70. Depression Guideline Panel. Clinical Practice Guideline, Number 5: Depression in Primary Care: Volume 2. Treatment of Major Depression. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research; 1993

71. Katon W, Russo J, Von Korff M, Lin E, Simon G, Bush T, Ludman E, Walker E. Long-term effects of a collaborative care intervention in persistently depressed primary care patients. J Gen Intern Med 2002;17: 741-748

72. Physician's Desk Reference, 59th ed. Montvale, NJ: Thompson PDR; 2005

73. Sachs GS, Thase ME, Otto MW, Bauer M, Miklowitz D, Wisniewski SR, Lavori P, Lebowitz B, Rudorfer M, Frank E, Nierenberg AA, Fava M, Bowden C, Ketter T,

Marangell L, Calabrese J, Kupfer D, Rosenbaum JF. Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry 2003;53: 1028-1042

74. Simon NM, Otto MW, Weiss RD, Bauer MS, Miyahara S, Wisniewski SR, Thase ME, Kogan J, Frank E, Nierenberg AA, Calabrese JR, Sachs GS, Pollack MH. Pharmacotherapy for bipolar disorder and comorbid conditions: baseline data from STEP-BD. J Clin Psychopharmacol 2004;24: 512-520

75. Perlis RH, Miyahara S, Marangell LB, Wisniewski SR, Ostacher M, DelBello MP, Bowden CL, Sachs GS, Nierenberg AA. Long-Term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry 2004;55: 875-881

76. Kraemer HC, Wilson T, Fairburn CG, Agras WS. Mediators and moderators of treatment effects in randomized controlled trials. Arch Gen Psychiatry 2002;59: 877-883

APPENDIX I

GENERAL PRINCIPLES FOR TREATMENT IMPLEMENTATION

- Clinical evaluation based on interview together with review of medical history form will be employed by study physicians to determine eligibility.
- 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(s) 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 4, assuming side effects are not problematic.
- Patients with QIDS-C_{16} scores below 6 may be maintained at the same dosage starting at week 4, 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(s) decreased, or continue the current dose(s) and manage the side effects.
- Treatment of secondary symptoms (see Appendix III)
- Some medications have a higher risk of unwanted symptoms if the medication is stopped abruptly. Physicians are advised to use caution and down titrate all medication dosages slowly
- If the dosing table suggests increasing one or both medications, the clinician may increase both medications simultaneously, or can increase only one of the combination medications. If increasing only one of the combination medications, the clinician is advised to first consider increasing the dosage of the primary medication, and to consider increasing the secondary medication in the combination as a second choice.
    - S-CIT + placebo: S-CIT (primary) + placebo (secondary)
    - BUP-SR + S-CIT: BUP-SR (primary) + S-CIT (secondary)
    - VEN-XR + MIRT: VEN-XR (primary) + MIRT (secondary)
- Patients having a less than 30% reduction in symptoms, as measured by the QIDS-C at weeks 8 and 10, may be considered for early study exit due to lack of treatment efficacy.

APPENDIX II

CRITICAL DECISION POINTS - DOSING TABLES

ESCITALOPRAM & PLACEBO

WEEK 0	ESCITALOPRAM & PLACEBO
Start Escitalopram 10 mg/day.	
Return to clinic:	Return in 1 week.

WEEK 1	ESCITALOPRAM & PLACEBO
Continue Escitalopram 10 mg/day	
SEs are significant*	Continue current dose and manage SEs.
SEs are intolerable*	Decrease dose, manage SE and continue for 1 week. *or* Exit if SE is not manageable.
Return to clinic:	Return in 1 week.

WEEK 2	ESCITALOPRAM & PLACEBO
Add 1 Placebo pill.	
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE is not manageable.
Return to clinic:	Return in 2 weeks.

*Use the FIBSER, and SAFTEE-SI as a guide. The QIDS-C_{16} total score is derived from the IDS-C_{30}.

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

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

*Use the FIBSER, and SAFTEE-SI as a guide. The QIDS-C_{16} total score is derived from the IDS-C_{30}.

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

WEEK 10	ESCITALOPRAM & PLACEBO
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Escitalopram to 20 mg/day *and/or* increase placebo to 2 pills.
QIDS-$C_{16} = 6\text{-}8$	Increase Escitalopram to 20 mg/day *and/or* increase placebo to 2 pills, *or* Continue current dose.
QIDS-$C_{16} \leq 5$	Continue current Escitalopram dosage, continue placebo dosage.
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE is not manageable.
Return to clinic:	Return in 2 weeks.

*Use the FIBSER, and SAFTEE-SI as a guide. The QIDS-C_{16} total score is derived from the IDS-C_{30}.

WEEK 12	ESCITALOPRAM & PLACEBO
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Escitalopram to 20 mg/day *and/or* increase placebo to 2 pills. See CRC for possible inclusion in Longer-term Phase.
QIDS-C_{16} = 6-8	Increase Escitalopram to 20 mg/day *and/or* increase placebo to 2 pills, *or* Continue current dosage. Enter Longer-term Phase.
QIDS-$C_{16} \leq 5$	Continue current Escitalopram dosage, continue placebo dosage. Enter Longer-term Phase.
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE is not manageable.
Return to clinic:	In 4 weeks if medication has not been changed during clinic visit *or* in 2 weeks if medication has been changed during clinic visit.

WEEKS 16, 20, 24	ESCITALOPRAM & PLACEBO
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Escitalopram to 20 mg/day *and/or* increase placebo to 2 pills..
QIDS-C_{16} = 6-8	Increase Escitalopram to 20 mg/day *and/or* increase placebo to 2 pills. *or* Continue current dose.
QIDS-$C_{16} \leq 5$	Continue current Escitalopram dosage, continue placebo dosage.
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE is not manageable.
Return to clinic:	In 4 weeks if medication has not been changed during clinic visit *or* in 2 weeks if medication has been changed during clinic visit.

*Use the FIBSER, and SAFTEE-SI as a guide. The QIDS-C_{16} total score is derived from the IDS-C_{30}.

WEEK 28	ESCITALOPRAM & PLACEBO
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:	Exit Study.

BUPROPION SR & ESCITALOPRAM

WEEK 0	BUPROPION SR & ESCITALOPRAM
Start Bupropion SR 150 mg/day.	
Return to clinic:	Return in 1 week.

WEEK 1	BUPROPION SR & ESCITALOPRAM
Increase Bupropion SR to 300 mg/day.	
SEs are significant*	Continue current dose and manage SEs.
SEs are intolerable*	Decrease dose, manage SE and continue for 1 week. *or* Exit if SE is not manageable.
Return to clinic:	Return in 1 week.

WEEK 2	BUPROPION SR & ESCITALOPRAM
Add Escitalopram 10 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 is not manageable.
Return to clinic:	Return in 2 weeks.

*****Use the FIBSER, and SAFTEE-SI as a guide. The QIDS-C_{16} total score is derived from the IDS-C_{30}.

WEEK 4	BUPROPION SR & ESCITALOPRAM
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Bupropion SR to 400mg/day *and/or* Escitalopram to 20 mg/day.
QIDS-$C_{16} = 6\text{-}8$	Increase Bupropion SR to 400mg/day *and/or* 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 is not manageable.
Return to clinic:	Return in 2 weeks.

WEEK 6	BUPROPION SR & ESCITALOPRAM
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Bupropion SR to 400mg/day *and/or* Escitalopram to 20 mg/day.
QIDS-$C_{16} = 6\text{-}8$	Increase Bupropion SR to 400mg/day *and/or* 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 is not manageable.
Return to clinic:	Return in 2 weeks.

*****Use the FIBSER, and SAFTEE-SI as a guide. The QIDS-C_{16} total score is derived from the IDS-C_{30}.

WEEK 8	BUPROPION SR & ESCITALOPRAM
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Bupropion SR to 400mg/day *and/or* Escitalopram to 20 mg/day.
QIDS-$C_{16} = 6\text{-}8$	Increase Bupropion SR to 400mg/day *and/or* 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 is not manageable.
Return to clinic:	Return in 2 weeks.

WEEK 10	BUPROPION SR & ESCITALOPRAM
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Bupropion SR to 400mg/day *and/or* Escitalopram to 20 mg/day.
QIDS-$C_{16} = 6\text{-}8$	Increase Bupropion SR to 400mg/day *and/or* 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 is not manageable.
Return to clinic:	Return in 2 weeks.

*****Use the FIBSER, and SAFTEE-SI as a guide. The QIDS-C_{16} total score is derived from the IDS-C_{30}.

WEEK 12	BUPROPION SR & ESCITALOPRAM
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Bupropion SR to 400mg/day *and/or* Escitalopram to 20 mg/day. See CRC for possible inclusion in Longer-term Phase.
QIDS-C_{16} = 6-8	Increase Bupropion SR to 400mg/day *and/or* Escitalopram to 20 mg/day *or* Continue current dose. Move to Longer-term Phase.
QIDS-$C_{16} \leq 5$	Continue current dose. Move to Longer-term Phase.
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE is not manageable.
Return to clinic:	In 4 weeks if medication has not been changed during clinic visit *or* in 2 weeks if medication has been changed during clinic visit.

WEEKS 16, 20, 24	BUPROPION SR & ESCITALOPRAM
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Bupropion SR to 400mg/day *and/or* Escitalopram to 20 mg/day.
QIDS-C_{16} = 6-8	Increase Bupropion SR to 400mg/day *and/or* 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 is not manageable.
Return to clinic:	In 4 weeks if medication has not been changed during clinic visit *or* in 2 weeks if medication has been changed during clinic visit.

*Use the FIBSER, and SAFTEE-SI as a guide. The QIDS-C_{16} total score is derived from the IDS-C_{30}.

WEEK 28	BUPROPION SR & 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:	Exit Study.

VENLAFAXINE XR & MIRTAZAPINE

WEEK 0	VENLAFAXINE XR & MIRTAZAPINE
Start Venlafaxine XR 37.5 mg/day for 3 days, then increase to 75 mg/day.	
Return to clinic:	Return in 1 week.

WEEK 1	VENLAFAXINE XR & MIRTAZAPINE
Increase Venlafaxine to 150 mg/day.	
SEs are significant*	Continue current dose and manage SE.
SEs are intolerable*	Decrease dose, manage SE and continue for 1 week. *or* Exit if SE is not manageable.
Return to clinic:	Return in 1 week.

WEEK 2	VENLAFAXINE XR & MIRTAZAPINE
Add Mirtazapine 15 mg/day.	
SEs are significant*	Continue current dose and manage SE.
SEs are intolerable*	Decrease dose, manage SE and continue for 1 week. *or* Exit if SE is not manageable.
Return to clinic:	Return in 2 weeks.

*Use the FIBSER, and SAFTEE-SI as a guide. The QIDS-C_{16} total score is derived from the IDS-C_{30}.

WEEK 4	VENLAFAXINE XR & MIRTAZAPINE
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Venlafaxine XR to 225mg/day *and/or* increase Mirtazapine to 30mg/day
QIDS-$C_{16} = 6\text{-}8$	Increase Venlafaxine XR to 225mg/day *and/or* increase Mirtazapine to 30mg/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 is not manageable.
Return to clinic:	Return in 2 weeks

WEEK 6	VENLAFAXINE XR & MIRTAZAPINE
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Venlafaxine XR to 225mg/day *and/or* increase Mirtazapine to 45mg/day
QIDS-$C_{16} = 6\text{-}8$	Increase Venlafaxine XR to 225mg/day and/or increase Mirtazapine to 45mg/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 is not manageable.
Return to clinic:	Return in 2 weeks.

*Use the FIBSER, and SAFTEE-SI as a guide. The QIDS-C_{16} total score is derived from the IDS-C_{30}.

WEEK 8	VENLAFAXINE XR & MIRTAZAPINE
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Venlafaxine XR to 300mg/day *and/or* increase Mirtazapine to 45mg/day
QIDS-$C_{16} = 6\text{-}8$	Increase Venlafaxine XR to 300mg/day *and/or* increase Mirtazapine to 45mg/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 is not manageable.
Return to clinic:	Return in 2 weeks.

WEEK 10	VENLAFAXINE XR & MIRTAZAPINE
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Venlafaxine XR to 300mg/day *and/or* increase Mirtazapine to 45mg/day
QIDS-$C_{16} = 6\text{-}8$	Increase Venlafaxine XR to 300mg/day *and/or* increase Mirtazapine to 45mg/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 is not manageable.
Return to clinic:	Return in 2 weeks.

*Use the FIBSER, and SAFTEE-SI as a guide. The QIDS-C_{16} total score is derived from the IDS-C_{30}.

WEEK 12	VENLAFAXINE XR & MIRTAZAPINE
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Venlafaxine XR to 300mg/day *and/or* increase Mirtazapine to 45mg/day. See CRC for possible inclusion in Longer-term Phase.
QIDS-$C_{16} = 6\text{-}8$	Increase Venlafaxine XR to 300mg/day *and/or* increase Mirtazapine to 45mg/day *or* Continue current dose. Move to Longer-term Phase.
QIDS-$C_{16} \leq 5$	Continue current dose. Move to Longer-term Phase.
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE is not manageable.
Return to clinic:	In 4 weeks if medication has not been changed during clinic visit *or* in 2 weeks if medication has been changed during clinic visit.

WEEKS 16, 20, 24	VENLAFAXINE XR & MIRTAZAPINE
Symptom Improvement *(SEs tolerable):*	
QIDS-$C_{16} \geq 9$	Increase Venlafaxine XR to 300mg/day *and/or* increase Mirtazapine to 45mg/day.
QIDS-$C_{16} = 6\text{-}8$	Increase Venlafaxine XR to 300mg/day *and/or* increase Mirtazapine to 45mg/day *or* Continue current dose.
QIDS-$C_{16} \leq 5$	Continue current dose. Move to Longer-term Phase.
SEs are significant*	Continue current dose and manage SE. *or* Decrease dose, manage SE and continue for 2 weeks.
SEs are intolerable*	Decrease dose, manage SE and continue for 2 weeks. *or* Exit if SE is not manageable.
Return to clinic:	In 4 weeks if medication has not been changed during clinic visit *or* in 2 weeks if medication has been changed during clinic visit.

*Use the FIBSER, and SAFTEE-SI as a guide. The QIDS-C_{16} total score is derived from the IDS-C_{30}.

WEEK 28	VENLAFAXINE XR & MIRTAZAPINE
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:	Exit Study.

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 will be adapted by the CRC and site staff to fit that site's operations.

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. The CRC must obtain written informed consent prior to performing any study-related procedures. Once the 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 longer-term phase of the study.
- 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 form:

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.

MEDICATION BLINDING

CO-MED is designed as a single blind (participant only), placebo controlled trial. The first medication given in each treatment cell will be open label (both participant and study personnel are unblinded). The second medication given in each treatment cell is blinded (participant only).

In the S-CIT + placebo treatment, the placebo medication is blinded; in the BUP-SR + S-CIT treatment cell, S-CIT is blinded; in the VEN-SR + MIRT treatment cell, MIRT is blinded. The blinded medications will be encapsulated (blinded) when distributed to sites. Participants will remain blind to the second study medication during both the short-term and the longer-term study.

CLINIC VISIT PROCEDURES

After signing informed consent and being screened, eligible participants will be seen for treatment and evaluated at Baseline (Week 0), and at Weeks 1, 2, 4, 6, 8, 10, and 12, and months 1, 2, 3, and 4 for participants enrolled in the longer-term phase. 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
- CDDF = Clinical and Demographic Data Form
- $HRSD_{17}$ = 17 item Hamilton Rating Scale for Depression
- M.I.N.I. = MINI International Neuropsychiatric Interview (MDD, Bipolar, and Psychosis Modules)
- EL = Eligibility form

BASELINE CLINIC VISIT

- Medication per Dosing Tables
- ASRM = Altman Self-Rating Mania Scale
- CMT = Concomitant Medication Tracking Form
- CPFQ = Cognitive and Physical Functioning Questionnaire
- PDSQ = Psychiatric Diagnostic Screening Questionnaire
- IDS-C_{30} = 30 item Inventory of Depressive Symptomatology – Clinician rated
- QIDS-SR_{16} = 16 item Quick Inventory of Depressive Symptomatology – Self-Report
- QOLI = Quality of Life Inventory
- RX = Study medication tracking form
- SAFTEE-SI = Systematic Assessment for Treatment Emergent Events-Specific Inquiry
- SCQ = Self-administered Comorbidity Questionnaire
- SRS = Suicidality Rating Scale
- SRS-AS = Suicidality Rating Scale-Associated Symptoms
- VS = Vital Signs (BP, P, weight)
- WPAI = The Work Productivity and Activity Impairment scale
- WSAS=Work and Social Adjustment Scale

WEEKS 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28

- Medication per Dosing Tables
- AQ = Adherence Questionnaire
- ASRM = Altman Self-Rating Mania Scale
- CMT = Concomitant Medication Tracking Form
- CPFQ = Cognitive and Physical Functioning Questionnaire
- FIBSER = Frequency, Intensity, and Burden Side Effects Rating
- IDS-C_{30} = 30 item Inventory of Depressive Symptomatology – Clinician rated
- QIDS-SR_{16} = 16 item Quick Inventory of Depressive Symptomatology – Self-Report
- QOLI = Quality of Life Inventory
- RX = Study medication tracking form
- SAFTEE-SI = Systematic Assessment for Treatment Emergent Events-Specific Inquiry
- SRS = Suicidality Rating Scale
- SRS-AS = Suicidality Rating Scale-Associated Symptoms
- VS = Vital Signs (BP, P, weight)
- WPAI = The Work Productivity and Activity Impairment Scale
- WSAS = Work and Social Adjustment Scale

TREATMENT OF SECONDARY SYMPTOMS

These rules apply to both the short-term and longer-term studies.

TREATMENTS FOR DEPRESSION. Only protocol medication treatments for depression are allowed. Other treatments that may have antidepressant effects are not allowed as they may confound our efforts to compare the short- and longer-term antidepressant effects of the protocol treatments. If other antidepressant treatments are used, the new treatment and protocol deviations will be recorded in the database (low dose trazodone is allowed for insomnia, $\leq$ 200 mg/day). Use of agents that are potential augmenting agents (e.g., T_3 in the absence of thyroid disease, SAMe, St. John's Wort, lithium, buspirone) is proscribed, as are antipsychotics, mood stabilizers, anticonvulsants (gabapentin, pregabalin, and topiramate are allowed for pain), and somatic therapies (e.g., rTMS, VNS, ECT). Depression-targeted, empirically validated psychotherapy for depression (e.g., cognitive therapy, IPT, CBASP, Problem-Solving Therapy, and light therapy) is proscribed, but other therapies (e.g., supportive, couples, occupational therapy) are allowed.

We will record all treatments received (psychotherapeutic, alternating somatic, psychopharmacological) during the short- and longer-term phases. The use of these treatments will be discouraged, but if these treatments are used in either the short- or longer-term phases, participants will continue in the study.

TREATMENT FOR GENERAL MEDICAL CONDITIONS. Any treatment for any GMC is allowed. S-CIT, MIRT, and VEN-XR are unlikely to produce drug-drug interactions based on P450 isoenzyme interactions, but BUP-SR is a moderate inhibitor of the 2D6 isoenzyme system. Study clinicians will be trained to recognize nonprotocol medications (e.g., Type 1C antiarrhthmics, beta blockers, etc.) for which serum levels or dose adjustments may be needed for these participants.

TREATMENTS FOR ANTIDEPRESSANT MEDICATION SIDE EFFECTS. Medications to treat antidepressant medication side effects are allowed so as to mimic practice and to increase retention. These side effects may be treated based on clinician judgment. The most common side effects are likely to be anxiety/agitation, insomnia, and sexual dysfunction. The following are suggested remedies for these side effects, but others are allowed within the bounds of the protocol.

INSOMNIA. Insomnia may be treated by watchful waiting/support, protocol medication dose adjustment, or zolpidem 5-10 mg qhs, eszopiclone 1-3 mg qhs, or a benzodiazepine hypnotic (e.g. temazepam 15-30 mg qhs) or trazodone (up to 200 mg/hs) at clinician discretion.

ANXIETY/AGITATION. Treatment emergent anxiety/agitation may be treated by watchful waiting/support, protocol medication dose adjustment, or clonazepam (0.5 to 2.0 mg/day) or lorazepam 0.5-2.0mg/day.

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

ADVERSE EVENTS

Medication side effects or adverse events can range from a minor annoyance to life-threatening situations. The more side effects that a participant is experiencing and the greater the daily interference that the side effects have on the participant's life, the less adherent to treatment participants are likely to be. Whether serious or not, it is important to track these side effects being experienced by each participant. In this study, side effects are assessed by self-rated questionnaires at each clinic visit. The following information will be reported to the Safety Officer within 24 hours of notification: pregnancy exposure, maternal or paternal exposure, lactation exposure, overdose, abuse, and inadvertent or accidental exposure to the study medication.

SERIOUS ADVERSE EVENTS (SAE)

An SAE is defined as any event during the course of the study that:

- Results in death
- Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Is a failed suicide attempt
- Requires inpatient hospitalization or prolongs existing hospitalization
- Results in a persistent or significant disability/incapacity
- Is medically significant
- Results in a congenital anomaly/birth defect
- Results in the development of drug dependency or drug abuse
- Results in cancer
- Furthermore, important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based

upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; the development of drug dependency or drug abuse.

REPORTING SAES

In the event of an SAE, the following procedures must be followed:

- A Serious Adverse Event form is to be completed and faxed to the Data Coordinating Center within 24 hours of the event becoming known to the Regional Center study personnel. The Data Coordinating Center will email this report to the Safety Officer, the Clinical Manager representing the PI, and the NIMH Representative.
- The Safety Officer, Dr. Ella Daly is available 24 hours a day/7 days a week to respond to reports of SAEs or any other safety issues). Dr. Madhukar Trivedi will be back up to Dr. Daly and is also available 24 hours a day/7 days a week).
- The Safety Officer will determine if the SAE is unexpected and/or related to study treatment. The Safety Officer will complete a SAE summary form, including these determinations and provide comment and recommendations to the Regional Center submitting the report.
- The safety officer is to report SAEs to the DSMB within 2 working days of notification of the safety officer.
- Any SAE that is determined by the Safety Officer to be related to a study drug and an unexpected event is to be reported to the FDA and pharmaceutical manufacturer by the Safety Officer within 24 hours using the MedWatch system (http://www.fda.gov/medwatch/report/instruct.htm).
- Other SAE reporting requirements of the pharmaceutical manufacturers supplying study drug will be followed.

APPENDIX IV

CRITERIA FOR NONRESPONSE TO ANTIDEPRESSANT TREATMENT TRIAL (USE WITH EXCLUSION CRITERIA)

LESS THAN A 50% REDUCTION IN DEPRESSIVE SYMPTOMS DURING AN ADEQUATE TREATMENT TRIAL OF ANTIDEPRESSANT MEDICATION (SEE BELOW).

ADEQUATE ANTIDEPRESSANT TREATMENT TRIAL

MEDICATION	DOSAGE / PER DAY	DURATION
Citalopram Fluoxetine Paroxetine	40 mg	6 weeks
Escitalopram	20 mg	6 weeks
Sertraline	150 mg	6 weeks
Paroxetine CR	37.5 mg	6 weeks
Fluvoxamine	150 mg	6 weeks
Duloxetine	90 mg	6 weeks
Venlafaxine XR	225 mg	6 weeks
Mirtazapine	30 mg	6 weeks
Bupropion	300 mg	6 weeks
Nortriptyline	75 mg	6 weeks
Protriptyline	30 mg	6 weeks

Amitriptyline Amoxapine Imipramine Desipramine Trimipramine Clomipramine Maprotilene Doxepin Nomifensine	150 mg	6 weeks
Isocarboxazid	30 mg	6 weeks
Tranylcypromine	40 mg	6 weeks
Phenelzine	90 mg	6 weeks
Trazodone	300 mg	6 weeks
Nefazodone	300 mg	6 weeks

APPENDIX V

STUDY ASSESSMENTS

CLINICAL, DEMOGRAPHIC, AND PRIOR TREATMENT HISTORY
Clinical/Demographic Data Form (CDDF)

MEASURES OF DEPRESSIVE SEVERITY
Hamilton Rating Scale for Depression ($HRSD_{17}$)
Inventory of Depressive Symptomatology - Clinician rated ($IDS\text{-}C_{30}$)
Quick Inventory of Depressive Symptomatology - Self-Report ($QIDS\text{-}SR_{16}$)

MEASURES OF PSYCHIATRIC COMORBIDITY
MINI International Neuropsychiatric Interview (M.I.N.I.)
Psychiatric Diagnostic Screening Questionnaire (PDSQ)
Altman Self-Rating Mania Scale (ASRM)
Cognitive and Physical Functioning Questionnaire (CPFQ)
Suicidality Rating Scale (SRS)
Suicidality Rating Scale - Associated Symptoms (SRS-AS)

MEASURES OF QUALITY OF LIFE
The Quality of Life Inventory (QOLI)
The Work Productivity and Activity Impairment scale (WPAI)
The Work and Social Adjustment Scale (WSAS)

MEASURES OF MEDICATION SIDE EFFECTS
Frequency, Intensity, and Burden Side Effects Rating (FIBSER)
Systematic Assessment for Treatment Emergent Events-Specific Inquiry (SAFTEE-SI)

MEASURES OF MEDICAL COMORBIDITIES
Self-administered Comorbidity Questionnaire (SCQ)

MEASURES OF ADHERENCE
Adherence Questionnaire (AQ)

MEDICATIONS
Study medication tracking form (RX)
Concomitant Medications Tracking Form (CMT)

PHYSICAL SYMPTOMS
Self-administered Comorbidity Questionnaire (SCQ)