

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med* 2006;354:1231-42.

Sequenced Treatment Alternatives

STAR★D

to Relieve Depression

***Clinical Procedures Manual***

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*Madhukar H. Trivedi, M.D.*

*Diane Stegman, RNC*

*A. John Rush, M.D.*

*Stephen R. Wisniewski, Ph.D.*

*Andrew A. Nierenberg, M.D.*



# Clinical Procedures Manual

<b>Overview of STAR★D</b>	Levels of Treatment	STAR★D At A Glance Table	Inclusion/Exclusion Criteria	General Principles	Treatment Implementation
	Medication Dosing Table	Side Effects/ Adverse Events	Clinical Research Coordinator	Data Management & Collection	Appendix

## Overview of STAR★D

At present, practitioners have a wide array of treatment options from which to choose when managing the care of patients with depression. These options include 20 Food and Drug Administration (FDA) approved antidepressant medications and 3 time-limited, scientifically tested psychotherapies. Even though a large number of treatment alternatives exist, no one treatment is effective for everyone, and many patients with depression do not experience a satisfactory clinical benefit from their initial treatment. In all, approximately 50% of patients benefit (i.e., have a response) from a standard first trial of an antidepressant medication. The remaining 50% (nonresponders to the initial treatment) must move on to the “next step” of treatment, in which patients receive some alternative to the initial failed trial. The most challenging task facing clinicians centers around choosing the next step once an initial treatment has not been effective.

STAR★D aims to determine the most effective treatment strategies and specific treatment options for patients with major depressive disorder who do not benefit adequately (symptom remission) from initial treatment with an antidepressant medication. The treatment protocol aims to determine and to implement an adequate dose and duration of medication (or psychotherapy) at every stage following the initial failed trial. STAR★D seeks to enroll 4,000 outpatients diagnosed with nonpsychotic, major depressive disorder. Fourteen Regional Centers across the United States will recruit these patients from primary and specialty care settings. Of these 4,000 patients, it is expected that approximately 2,000 patients will not have a satisfactory response to the first antidepressant. Nonresponders as well as those who respond but who do not attain remission are eligible for seven different treatment options at the next treatment step (Level 2). These options also include one time-limited psychotherapy.

The patient and clinician will determine, from the treatment options available, which ones would be acceptable, beneficial, and medically safe. Patients will be randomized to one of all acceptable treatment options.

Patients who do not have a satisfactory therapeutic response to Level 2 treatment will be presented with four treatment options as a third step (Level 3). As in the previous level, patients will be randomly assigned to one of the acceptable options at Level 3. Consistent with Levels 2 and 3, at Level 4, two treatment options will be provided (using randomization) for patients who have not responded satisfactorily to the previous level of treatment.

STAR★D will (1) compare the effectiveness of selected treatment options and, consequently, treatment sequences in reducing patients’ symptoms and improving their function, and (2) define the costs and cost offsets of such care.



While both patients and clinicians will know of all the available treatment options, independent assessors, masked to treatment type, will evaluate research outcomes. Research outcomes include measures of depressive and associated symptoms, work performance, functioning, quality of life, patient satisfaction, and service utilization.

Once patients' depressive symptoms have remitted, or at least responded, they will enter the 12-month naturalistic follow-up. By including a follow-up phase, we will be able to determine the occurrence and timing of relapse associated with specific treatment strategies.

By recruiting a large, widely representative group of outpatients with major depressive disorder, STAR★D will generate information that will be directly applicable to current practice. STAR★D will develop and implement patient/family education materials, as well as practical guidelines for clinicians to follow when implementing evidence-based treatment steps in the care of depressed patients.

The National Coordinating Center (NCC) for the study (University of Texas Southwestern Medical Center at Dallas) will oversee the implementation of the protocol at the 14 Regional Centers. Each center will coordinate the care at 2-4 clinical settings or sites where clinicians working in both private and public sectors providing either primary or specialty care will enroll and treat study participants. Key collaborating institutions include Massachusetts General Hospital (Boston), University of Pittsburgh Medical Center and Western Psychiatric Institute and Clinic (Pittsburgh), University of Pittsburgh's Epidemiology Data Center (Pittsburgh) and Columbia College of Physicians and Surgeons (New York).



# Clinical Procedures Manual

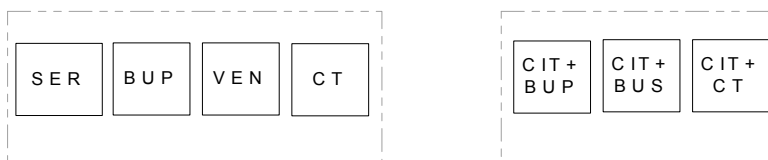
Overview of STAR★D	<b>Levels of Treatment</b>	STAR★D At A Glance Table	Inclusion/Exclusion Criteria	General Principles	Treatment Implementation
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## Levels of Treatment

**Figure 1: Treatment Options by Level**

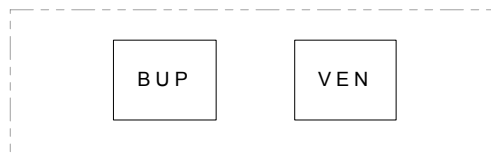
### Level 2:

**Treatment Options**



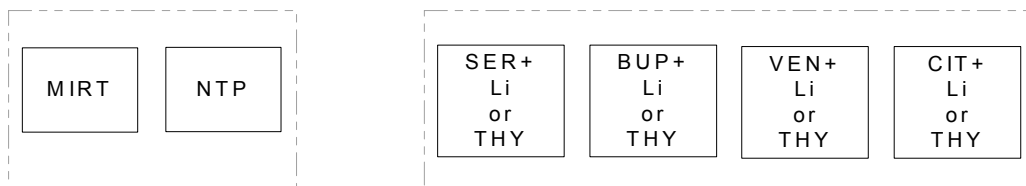
### Level 2A:

**Treatment Options**



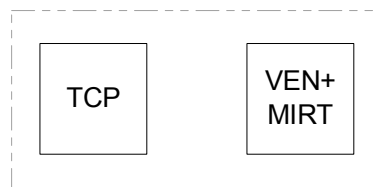
### Level 3:

**Treatment Options**



### Level 4:

**Treatment Options**



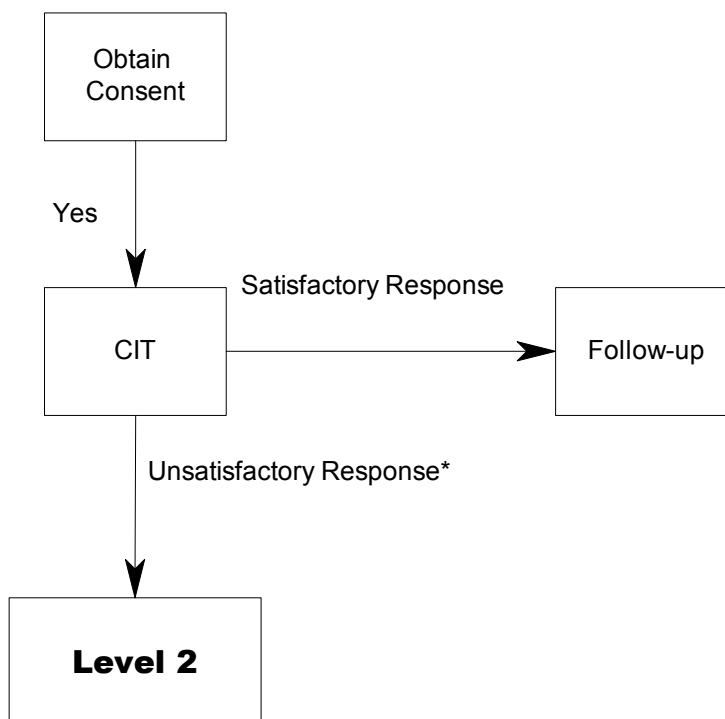
BUP = Bupropion  
 BUS = Buspirone  
 CIT = Citalopram  
 CT = Cognitive Therapy

Li = Lithium  
 MIRT = Mirtazapine  
 NTP = Nortriptyline  
 SER = Sertraline

TCP = Tranylcypromine  
 THY = Thyroid  
 VEN = Venlafaxine



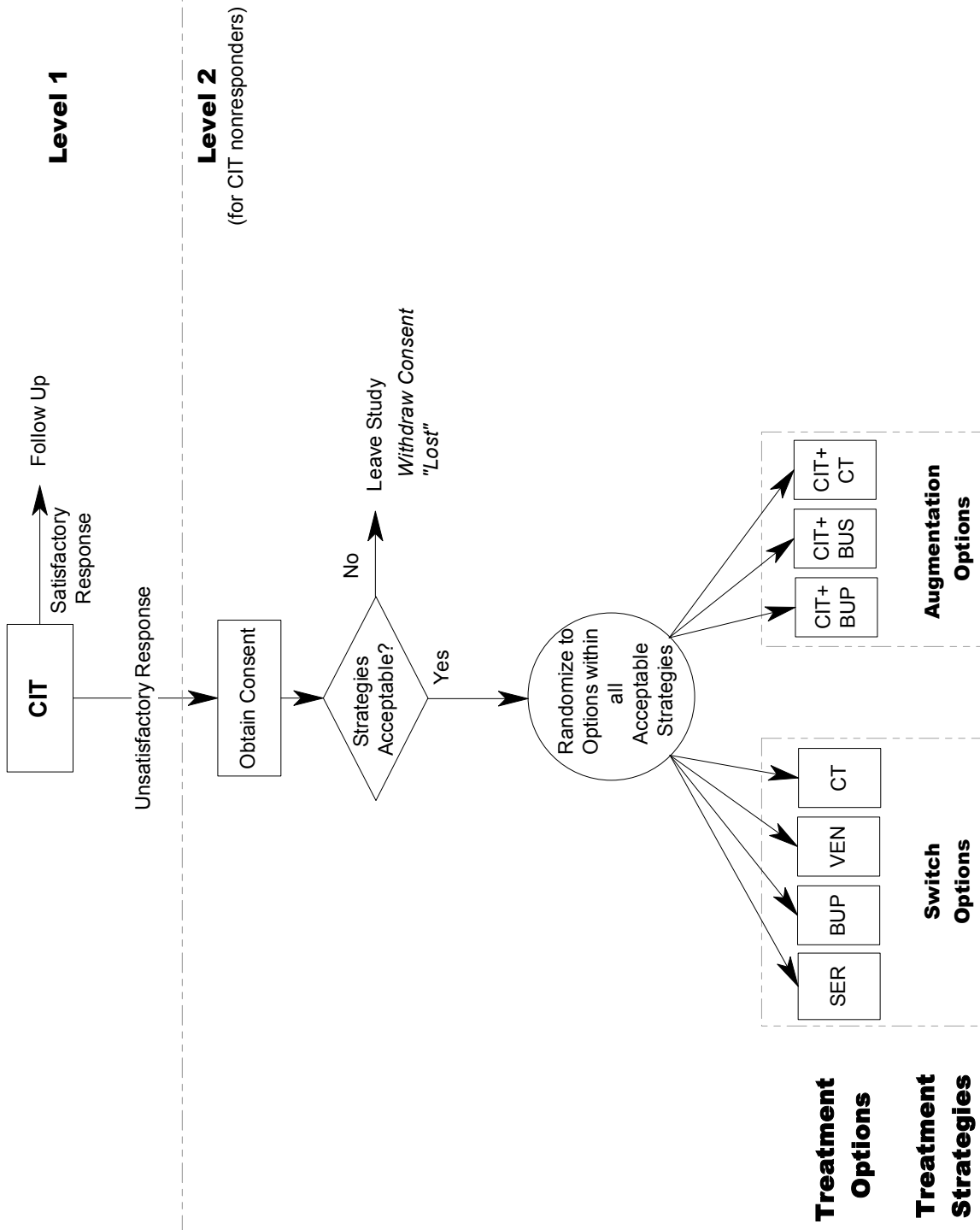
**Figure 2: Entry and Level 1**



\* Defined as nonremission.



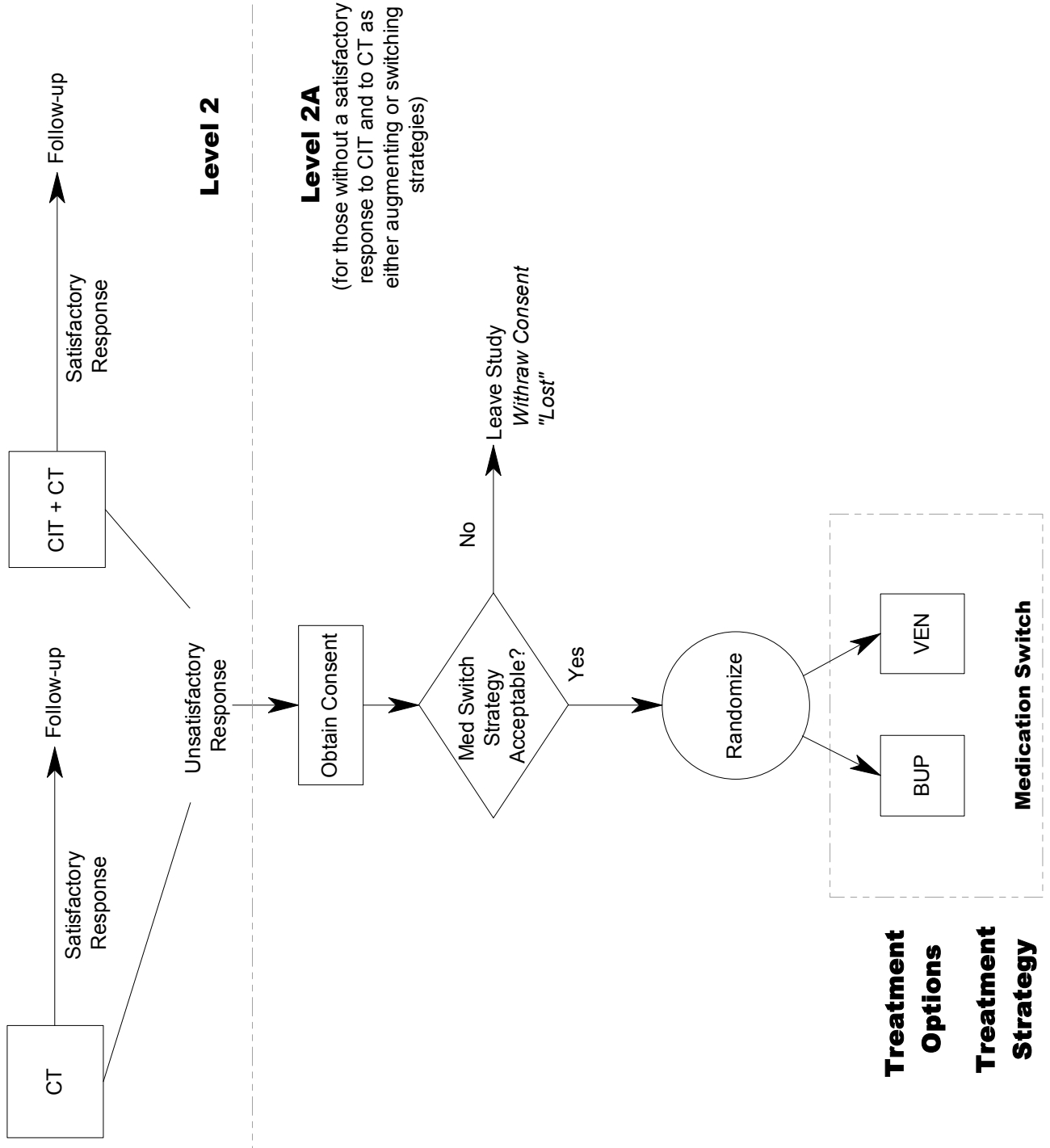
**Figure 3: Level 2**



\* If strategy group is not acceptable to the patient, then patient is randomized to treatment options within remaining acceptable treatment strategies. If all treatment strategies are rejected, then patient enters naturalistic follow-up.

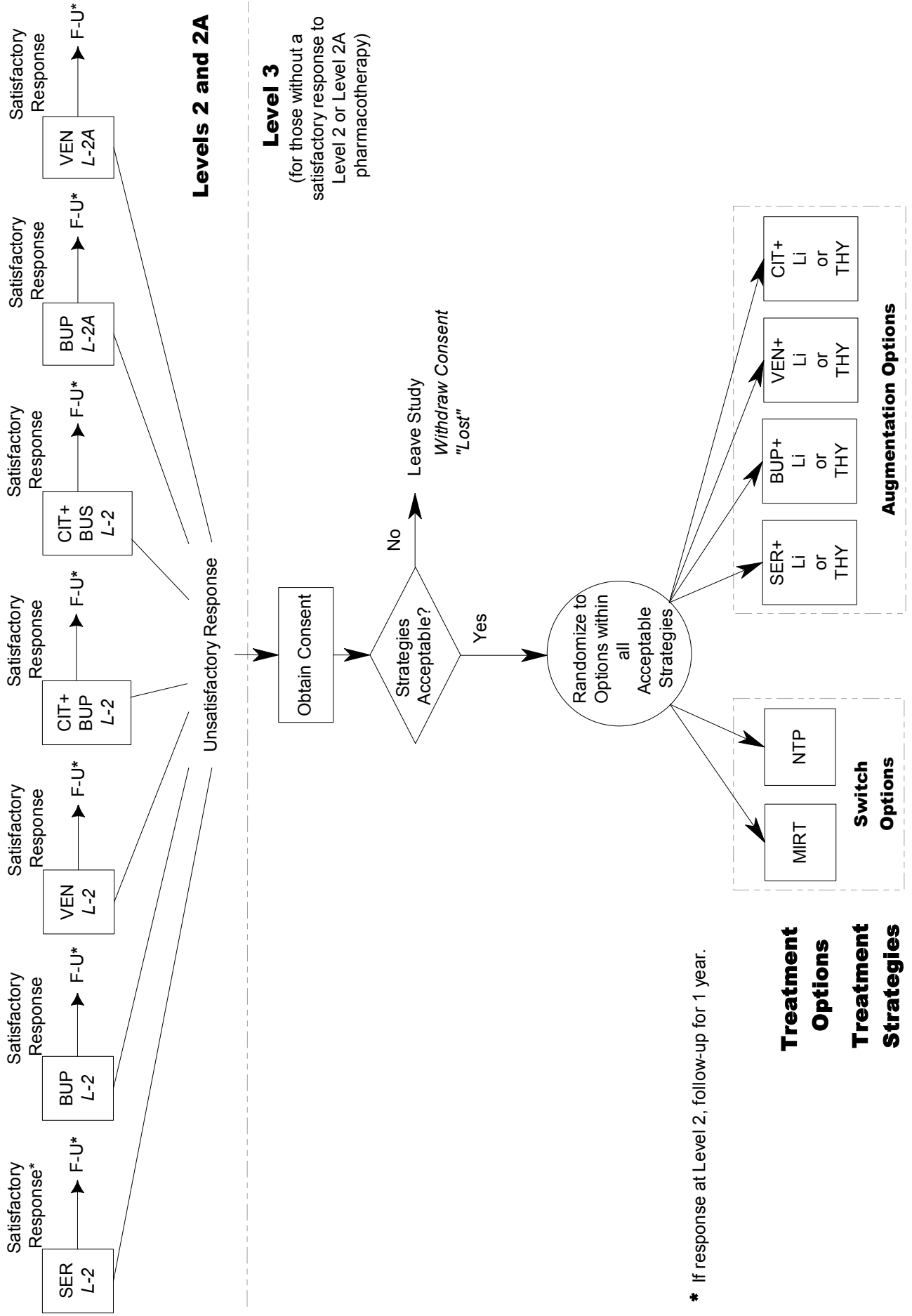


**Figure 4: Level 2A**



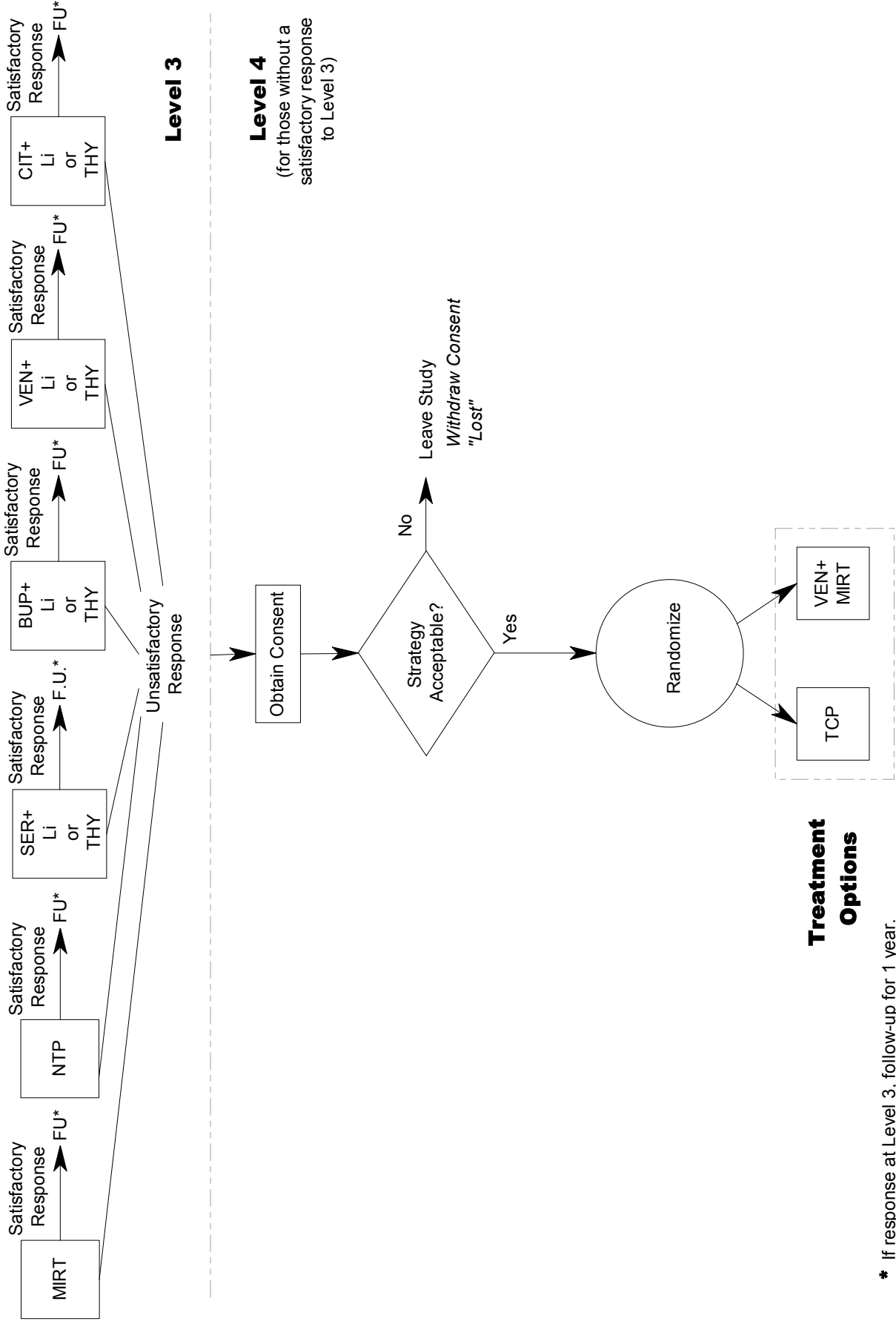


**Figure 5: Level 3**





**Figure 6: Level 4**



\* If response at Level 3, follow-up for 1 year.



# Clinical Procedures Manual

Overview of STAR★D	Levels of Treatment	<b>STAR★D At A Glance Table</b>	Inclusion/Exclusion Criteria	General Principles	Treatment Implementation
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## STAR★D Treatment At-a-Glance

**Visit Frequency:** Clinic visits will be at weeks 0, 2, 4, 6, 9, and 12 of each level or until remission or adequate response is obtained.

**Duration of Acute Treatment:** Acute treatment will be at least 6 weeks if remission occurs, or up to 12 weeks; remission will be sustained for 2 weeks before moving on to the continuation phase.

*\*If the patient has had a good response, but has not remitted at Week 12, and the clinician feels that 2 more weeks of treatment would be beneficial, treatment may be extended for 2 more weeks.*

**Response:** Clinicians will determine response with the 16-item Quick Inventory of Depressive Symptomatology (QIDS-C<sub>16</sub>) using the following guidelines:

Nonresponse	QIDS-C <sub>16</sub> ≥ 9
Partial response	QIDS-C <sub>16</sub> = 6-8
Remission	QIDS-C <sub>16</sub> ≤ 5

**Criteria for Medication Change:** QIDS-C<sub>16</sub> = 6-8 may require a dosage change or move to next level.

**Evaluations:** At each visit, the Clinical Research Coordinator (CRC) will assess patients before the patients see the clinician; these assessments will include the QIDS-C<sub>16</sub> and patient self-rating of symptom severity (QIDS-SR<sub>16</sub>) and side effects. After the CRC evaluation, the clinician will assess core symptom severity, overall functional impairment, and side effect severity.

**Medication Doses:** See Medication Dosing Table and the Guidelines in Appendix C for information on medications.

*Note: Doses outside of the ranges should have a chart note indicating “change from protocol recommended” and documentation of rationale for change.*



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# Clinical Procedures Manual

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## **Inclusion/Exclusion Criteria**

### **Inclusion Criteria**

- ★ Age 18–75.
- ★ Written informed consent completed.
- ★ Scores 14 or higher on the 17-item Hamilton Depression Rating Scale.
- ★ Initial treatment with medication is clinically appropriate.
- ★ Meets DSM-IV criteria for single or recurrent nonpsychotic MDD.

*Note: Suicidal patients are eligible, as long as outpatient treatment is deemed safe by the clinician, as are patients who have any of most general medical conditions (GMCs).*

### **Exclusion Criteria**

- ★ History of bipolar disorder (I, II, or NOS) (lifetime).
- ★ History of schizophrenia, schizoaffective disorder, or psychosis NOS (lifetime).
- ★ Current anorexia nervosa or bulimia nervosa.
- ★ Current primary obsessive-compulsive disorder (OCD).
- ★ History of clear-cut intolerability to, or lack of effect with, an adequate trial (e.g., 60 mg of fluoxetine for 6 weeks) of at least one protocol medication in the current episode of MDD.
- ★ Lack of response to an adequate trial of an SSRI (citalopram, fluoxetine, paroxetine, and sertraline) in the current episode of MDD (e.g., adequate trial with citalopram is at least 40 mg/day for six weeks or 60 mg/day for the last two weeks of a six-week trial).
- ★ Is currently taking citalopram at 20mg or more and has been taking it for more than 14 days.
- ★ Is currently taking escitalopram at any dose and has been taking it for more than 14 days.
- ★ Did not respond to 16 or more sessions of cognitive therapy in the current episode of MDD.
- ★ Did not respond to 7 or more sessions of ECT in the current episode of MDD.



- ★ Has general medical condition, which contraindicates any level 1 or 2 treatment option.
- ★ Is on concomitant medication, which contraindicates any level 1 or 2 treatment option.
- ★ Needs hospitalization now for substance/alcohol detoxification or treatment.
- ★ Needs hospitalization now for psychiatric disorder(s).
- ★ Requires antipsychotic medications or mood stabilizers.
- ★ Is pregnant or breast feeding.
- ★ Patients currently taking any of the following exclusionary medications:

Antipsychotic medications

Anticonvulsant medications

Mood stabilizers

Central Nervous System stimulants

Antidepressant medications:

ض Used for the treatment of depression.

ض Used for other purposes, e.g., Zyban for smoking cessation, Seraphim for premenstrual dysphoric disorder.

*In general, patients who are on other concomitant medications will enter the study as long as their clinician determines that antidepressant treatment with citalopram and all other medications in the algorithm is appropriate and safe.*

*Patients taking thyroid medication for hypothyroidism may be included if they have been stable on the medication for 3 months. **Patients who are diagnosed with Hypothyroidism after entering the study may remain in the study. Patients on thyroid supplement for Hypothyroidism may take Cytomel if randomized to it in Level 3.***

Patients can participate in a modality of psychotherapy that is not targeting the symptoms of depression (e.g., supportive therapy, marital therapy).

Therapy that is depression specific, such as Cognitive Therapy (CT) or Interpersonal Psychotherapy of Depression (IPT) is not allowed prior to or during participation, unless it is the assigned and delivered study treatment.



The following statements apply when determining eligibility for patients who have participated in a clinical drug trial during the current episode of depression:

- ★ Prior participation in the current episode in a placebo-controlled blind trial with non-psychotropic drugs (e.g., cholesterol-lowering drugs): eligible.
- ★ Prior participation in the current episode in a placebo-controlled blind trial with psychotropic drugs not yet approved by the FDA for depression: eligible.
- ★ Prior participation in the current episode in a placebo-controlled blind trial with an SSRI or other psychotropic drugs that are part of STAR\*D: not eligible.
- ★ Current participation in a placebo-controlled blind trial with psychotropic drugs or exclusionary drugs: not eligible.
- ★ Current participation in a placebo-controlled blind trial with non-psychotropic drugs (e.g., cholesterol-lowering drugs): eligible.



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## *General Principles for Treatment Implementation*

- ★ The ultimate goals in the acute phase of treatment (0-12 weeks) are achieving symptomatic remission and full return of psychosocial functioning. The prevention of relapse and recurrence are the essential goals of follow-up treatment.
- ★ Strategies are the groupings of specific treatments, i.e., medication augmentation, psychotherapy switch; options are the specific treatments within the strategy, i.e., sertraline, cognitive therapy.
- ★ Critical Decision Points (CDPs) are designed to prompt an assessment of symptoms and a determination of a need for a change in tactics or level. At each CDP, the physician should assess the patient for improvement and make a decision to either continue or change treatment based on improvement in symptoms or lack thereof.
- ★ At the beginning of each level, follow-up visits should be scheduled at weeks 2, 4, 6, 9, and 12. The increased frequency of visits has been noted to optimize treatment outcomes by: a) encouraging patient adherence with treatment and b) rapidly identifying and correcting potential problems or adverse events associated with treatment.
- ★ Response to a medication is enhanced by ensuring an adequate treatment trial of at least 4-8 weeks of administration at the recommended dosage range. However, if a patient fails to respond to an adequate dosage of a specific medication for 4-6 weeks or has an unsatisfactory or partial response by weeks 6-8, an alternative treatment plan is recommended.
- ★ If the patient experiences intolerable side effects after the initial dose or dose adjustment, the dosage may be decreased.
- ★ The one-year naturalistic follow-up treatment is recommended to prevent relapse for all patients with major depressive disorders who achieve a satisfactory clinical response, preferably symptom remission.
- ★ Adjunctive medications prescribed for the treatment of associated symptoms such as anxiety or treatment-emergent side effects should be discontinued once these symptoms resolve. The rationale for their use should be carefully documented. The continued indication for these medications should be reassessed on a regular basis.
- ★ As a part of general treatment of depressive patients during diagnosis and ongoing evaluation, the presence of suicidal ideation and/or intent should be assessed throughout acute phase and follow-up treatment. If during a clinic visit or telephone call a patient indicates that he/she is having suicidal thoughts and appears to be at risk for committing suicide, i.e., has a plan, certain steps should be taken. Please see Suicide Procedures.



### ***Critical Decision Points (CDPs) and Tactics for Acute Phase Treatment of Major Depression***

<b>Critical Decision Point</b>	<b>Clinical Status</b>	<b>Plan</b>
Week 0 (CDP #1)	Symptomatic	<ul style="list-style-type: none"> <li>◆ Initiate medication; adjust dose to lower end of therapeutic dose range or serum level.</li> </ul>
Week 4 (CDP #2)	Remission (QIDS-C <sub>16</sub> ≤ 5)	<ul style="list-style-type: none"> <li>◆ Continue current dose.</li> </ul>
	Partial Response (QIDS-C <sub>16</sub> = 6-8)	<ul style="list-style-type: none"> <li>◆ Continue current dose.</li> <li>◆ Consider increasing dose.</li> </ul>
	Nonresponse (QIDS-C <sub>16</sub> ≥ 9)	<ul style="list-style-type: none"> <li>◆ Increase dose.</li> </ul>
	Remission (QIDS-C <sub>16</sub> ≤ 5)	<ul style="list-style-type: none"> <li>◆ Continue current dose.</li> </ul>
Week 6 (CDP #3)	Partial Response (QIDS-C <sub>16</sub> = 6-8)/ Nonresponse (QIDS-C <sub>16</sub> ≥ 9)	<ul style="list-style-type: none"> <li>◆ Increase/Maximize dose.</li> </ul>
	Remission (QIDS-C <sub>16</sub> ≤ 5)	<ul style="list-style-type: none"> <li>◆ Continue current dose.</li> </ul>
Week 9 (CDP #4)	Remission (QIDS-C <sub>16</sub> ≤ 5)	<ul style="list-style-type: none"> <li>◆ Continue current dose.</li> </ul>
	Partial Response (QIDS-C <sub>16</sub> = 6-8)	<ul style="list-style-type: none"> <li>◆ Increase dose.</li> <li>◆ Go to the next level.</li> </ul>
	Nonresponse (QIDS-C <sub>16</sub> ≥ 9)	<ul style="list-style-type: none"> <li>◆ Discontinue and go to the next level.</li> </ul>
	Remission (QIDS-C <sub>16</sub> ≤ 5)	<ul style="list-style-type: none"> <li>◆ Go to follow-up phase.</li> </ul>
Week 12 (CDP #5)	Partial Response (QIDS-C <sub>16</sub> = 6-8)	<ul style="list-style-type: none"> <li>◆ Go to the next level.</li> <li>◆ Increase dose and reevaluate in 2 weeks.</li> </ul>

*\*If the patient has had a good response, but has not remitted at Week 12, and the clinician feels that 2 more weeks of treatment would be beneficial, treatment may be extended for 2 more weeks.*



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## Treatment Implementation

### Level 1

All patients entering Level 1 will be started on citalopram.

Patients may enter the study currently taking citalopram for up to two weeks. If a patient is entering the study currently on citalopram, the treatment is guided by utilizing the CDPs according to how long the patient has been on the medication.

For example: If the patient has been on citalopram 20 mg for 2 weeks, the patient will return in two weeks for the week 2 visit. However, the treatment will be guided by the week 4 Critical Decision Point.

#### CDP, Week 0

STAR★D Level 1

**Start patient on citalopram 20 mg/day**

Return to clinic:

Return in 2 weeks.

#### CDP, Week 4

STAR★D Level 1

**Symptom Improvement (SEs tolerable)**

QIDS-C<sub>16</sub> ≥ 9

Increase dose to 40 mg/day.

QIDS-C<sub>16</sub> = 6-8

Continue current dose, *or*  
Increase dose to 40 mg/day.

QIDS-C<sub>16</sub> ≤ 5

Continue current dose.

**Improved, but SEs are intolerable**

Continue current dose and address SEs, *or*  
Go to the next level.

**Not improved and SEs are intolerable**

Go to the next level.

Return to clinic:

Return in 2 weeks.



**CDP, Week 6** **STAR★D Level 1**

**Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Increase dose to 60 mg/day.
QIDS-C <sub>16</sub> = 6-8	Increase dose to 60mg/day, <i>or</i> Continue current dose.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<b>Improved, but SEs are intolerable</b>	Continue current dose and address SEs, <i>or</i> Decrease dose and continue for 2 additional weeks, <i>or</i> Go to the next level.
<b>Not improved and SEs are intolerable</b>	Go to the next level.
Return to clinic:	Return in 3 weeks.

**CDP, Week 9** **STAR★D Level 1**

**Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Increase dose to 60 mg/day, if not done previously, <i>or</i> Go to next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<b>SEs are intolerable</b>	Go to the next level.
Return to clinic:	Return in 3 weeks.

**CDP, Week 12** **STAR★D Level 1**

**Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Continue current dose and go to follow-up, <sup>1</sup> <i>or</i> Go to the next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose and go to follow-up.
<b>SEs are intolerable</b>	Go to the next level.
Return to clinic:	If remitted, <ul style="list-style-type: none"> <li>• Return in 3 months or as needed.</li> </ul> If starting new level <ul style="list-style-type: none"> <li>• Return in 2 weeks.</li> </ul>

<sup>1</sup> Because of the severity of some patients, clinicians may choose to keep patient on current dose and move to follow-up if at week 12 the patient has maintained a score of 6-8 on the QIDS-C or if the patient does not want to change medications and/or the patient is satisfied with the level of improvement.



## **Level 2**

Upon entry to Level 2, the clinician will discuss with the patient the options at Level 2 to determine patient acceptability. The patient will then be randomized to one option that is deemed acceptable and medically safe. Refer to the appropriate treatment table for each option.

### **Level 2 Treatment Strategies/Options**

1) Augment the citalopram with either other medications or psychotherapy.

#### **Medication or Psychotherapy Augmentation**

- BupropionSR (BUP)
- Buspirone (BUS)
- Cognitive Therapy (CT)

2) Switch to a different antidepressant or psychotherapy.

#### **Medication or Psychotherapy Switch**

- Sertraline (SER)
- BupropionSR (BUP)
- VenlafaxineXR (VEN)
- Cognitive Therapy (CT)

3) Add psychotherapy to the citalopram or discontinue citalopram and switch to psychotherapy.

#### **Psychotherapy Augmentation or Switch**

- Add Cognitive Therapy (CT)
- Switch to Cognitive Therapy (CT)

4) Switch to a different antidepressant but not to psychotherapy.

#### **Medication Switch Only**

- Sertraline (SER)
- BupropionSR (BUP)
- VenlafaxineXR (VEN)

5) Augment the citalopram with other medications but not psychotherapy.

#### **Medication Augmentation Only**

- BupropionSR (BUP)
- Buspirone (BUS)



6) Augment the citalopram with other medications or switch to other medications without any psychotherapy.

**Medication Augmentation**

- BupropionSR (BUP)
- Buspirone (BUS)

**Or**

**Medication Switch**

- Sertraline (SER)
- BupropionSR (BUP)
- VenlafaxineXR (VEN)



## **Level 2 – Psychotherapy Switch**

If the patient has been randomized to psychotherapy switch, refer the patient to the STAR★D cognitive therapist. The therapist will continue to follow the patient and implement the protocol.

## **Level 2 – Psychotherapy Augmentation**

If the patient has been randomized to psychotherapy augmentation, refer the patient to the STAR★D cognitive therapist and continue on current citalopram dose.

## **Level 2A**

Patients that were randomized to either psychotherapy option (switch or augmentation) and did not respond adequately will move to Level 2A. Refer to the appropriate treatment table for each option.

## **Level 2A Treatment Strategies/Options**

### **Medication Switch**

- BupropionSR (BUP)
- VenlafaxineXR (VEN)

## **Level 3**

Upon entry to Level 3, the clinician will discuss with the patient the options available at this level to determine patient acceptability. The patient will then be randomized to one option that is deemed acceptable and medically safe. Refer to the appropriate treatment table for each option. If the patient has been treated by a primary care clinician during Level 1 and Level 2 and it is determined that the patient should be treated at a Specialty Clinic for Level 3, the following steps are to be taken:

- a. Randomize the patient at the time the determination is made to go to Level 3.
- b. Have the patient seen in the Specialty Clinic within 2 days, OR
- c. Prescribe the Level 3 medication and the Regional Director or Associate Director will assume the patient's care until they can be seen in the Specialty Clinic.

The patient should know at all times who his treating clinician is and how to contact him.

## **Level 3 Treatment Strategies/Options**

- 1) Augment the current (Level 1 or 2) antidepressant with either lithium (Li) or thyroid (THY). When citalopram is augmented with bupropion in Level 2, and the patient again allows for augmentation in Level 3, the citalopram will be augmented with lithium or thyroid.



### **Medication Augmentation**

- Lithium (Li)
- Thyroid (THY)

2) Switch to a different antidepressant

### **Medication Switch**

- Mirtazapine (MIRT)
- Nortriptyline (NTP)



## Levels 2 – 3 - Medication Switch Sertraline

CDP, Week 0	STAR☆D Levels 2 - 3 - Sertraline
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Start patient on sertraline 50 mg/day for 2 weeks, then 100 mg/day

Return to clinic: Return in 2 weeks.

CDP, Week 4	STAR☆D Levels 2 - 3 - Sertraline
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*Symptom Improvement (SEs tolerable)*

QIDS-C <sub>16</sub> ≥ 9	Increase dose to 150 mg/day.
QIDS-C <sub>16</sub> = 6-8	Continue current dose, <i>or</i> Increase dose to 150 mg/day.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<i>Improved, but SEs are intolerable</i>	Continue current dose and address SEs, <i>or</i> Go to the next level.
<i>Not improved and SEs are intolerable</i>	Go to the next level.

Return to clinic: Return in 2 weeks.

CDP, Week 6	STAR☆D Levels 2 - 3 - Sertraline
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*Symptom Improvement (SEs tolerable):*

QIDS-C <sub>16</sub> ≥ 9	Increase dose to 150 mg/day.
QIDS-C <sub>16</sub> = 6-8	Increase dose to 150 mg/day, if not done previously <i>or</i> continue current dose.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<i>Improved, but SEs are intolerable</i>	Continue current dose and address SEs, <i>or</i> Decrease dose and continue for 2 additional weeks, <i>or</i> Go to the next level.
<i>Not improved and SEs are intolerable</i>	Go to the next level.

Return to clinic: Return in 3 weeks.

**CDP, Week 9****STAR☆D Levels 2 - 3 - Sertraline****Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Increase dose to 200 mg/day <i>or</i> Go to next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<b>SEs are intolerable</b>	Go to the next level.
Return to clinic:	Return in 3 weeks.

**CDP, Week 12****STAR☆D Levels 2 - 3 - Sertraline****Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Continue current dose and go to follow-up <sup>1</sup> , <i>or</i> Go to the next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose and go to follow-up.
<b>SEs are intolerable</b>	Go to the next level.
Return to clinic:	If remitted, <ul style="list-style-type: none"><li>• Return in 3 months or as needed.</li></ul> If starting new level <ul style="list-style-type: none"><li>• Return in 2 weeks.</li></ul>

<sup>1</sup> Because of the severity of some patients, clinicians may choose to keep patient on current dose and move to follow-up if at week 12 the patient has maintained a score of 6-8 on the QIDS-C or if the patient does not want to change medications and/or the patient is satisfied with the level of improvement.



## Levels 2 – 2A - Medication Switch BupropionSR

<b>CDP, Week 0</b>	<b>STAR★D Levels 2 - 2A - 3 - BupropionSR</b>
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Start patient on BupropionSR 150 mg/day for 7 days, then 200 mg/day

Return to clinic: Return in 2 weeks.

<b>CDP, Week 4</b>	<b>STAR★D Levels 2 - 2A - 3 - BupropionSR</b>
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*Symptom Improvement (SEs tolerable)*

QIDS-C <sub>16</sub> ≥ 9	Increase dose to 300 mg/day.
QIDS-C <sub>16</sub> = 6-8	Continue current dose, <i>or</i> Increase dose to 300 mg/day.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<i>Improved, but SEs are intolerable</i>	Continue current dose and address SEs, <i>or</i> Go to the next level.
<i>Not improved and SEs are intolerable</i>	Go to the next level.

Return to clinic: Return in 2 weeks.

<b>CDP, Week 6</b>	<b>STAR★D Levels 2 - 2A - 3 - BupropionSR</b>
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*Symptom Improvement (SEs tolerable):*

QIDS-C <sub>16</sub> ≥ 9	Increase dose to 400 mg/day.
QIDS-C <sub>16</sub> = 6-8	Increase dose to 400 mg/day, <i>or</i> Continue current dose.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<i>Improved, but SEs are intolerable</i>	Continue current dose and address SEs, <i>or</i> Decrease dose and continue for 2 additional weeks, <i>or</i> Go to the next level.
<i>Not improved and SEs are intolerable</i>	Go to the next level.

Return to clinic: Return in 3 weeks or as needed.

**CDP, Week 9****STAR☆D Levels 2 - 2A - 3 – BupropionSR****Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Increase dose to 400 mg/day, if not done previously, <i>or</i> Go to next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<b>SEs are intolerable</b>	Go to the next level.
Return to clinic:	Return in 3 weeks.

**CDP, Week 12****STAR☆D Levels 2 - 2A - 3 - BupropionSR****Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Continue current dose and go to follow-up <sup>1</sup> , <i>or</i> Go to the next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose and go to follow-up.
<b>SEs are intolerable</b>	Go to the next level.
Return to clinic:	If remitted, <ul style="list-style-type: none"><li>• Return in 3 months or as needed.</li></ul> If starting new level <ul style="list-style-type: none"><li>• Return in 2 weeks.</li></ul>

<sup>1</sup> Because of the severity of some patients, clinicians may choose to keep patient on current dose and move to follow-up if at week 12 the patient has maintained a score of 6-8 on the QIDS-C or if the patient does not want to change medications and/or the patient is satisfied with the level of improvement.



## Levels 2 – 2A – 3 - Medication Switch Venlafaxine

CDP, Week 0

STAR★D Levels 2 - 2A - 3 - VenlafaxineXR

Start patient on venlafaxineXR 37.5 for 7 days, then 75 mg/day for 7days, then 150 mg/day

Return to clinic:

Return in 2 weeks.

CDP, Week 4

STAR★D Levels 2 - 2A - 3 - VenlafaxineXR

*Symptom Improvement (SEs tolerable)*

QIDS-C<sub>16</sub> ≥ 9

Increase dose to 225 mg/day.

QIDS-C<sub>16</sub> = 6-8

Continue current dose, *or*  
Increase dose to 225 mg/day.

QIDS-C<sub>16</sub> ≤ 5

Continue current dose.

*Improved, but SEs are intolerable*

Continue current dose and address SEs, *or*  
Go to the next level.

*Not improved and SEs are intolerable*

Go to the next level.

Return to clinic:

Return in 2 weeks.

CDP, Week 6

STAR★D Levels 2 - 2A - 3 - VenlafaxineXR

*Symptom Improvement (SEs tolerable):*

QIDS-C<sub>16</sub> ≥ 9

Increase dose to 300 mg/day.

QIDS-C<sub>16</sub> = 6-8

Increase dose to 300 mg/day, *or*  
Continue current dose.

QIDS-C<sub>16</sub> ≤ 5

Continue current dose.

*Improved, but SEs are intolerable*

Continue current dose and address SEs, *or*  
Decrease dose and continue for 2 additional weeks, *or*  
Go to the next level.

*Not improved and SEs are intolerable*

Go to the next level.

Return to clinic:

Return in 3 weeks.

**CDP, Week 9****STAR★D Levels 2 - 2A - 3 - VenlafaxineXR****Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Increase dose to 375 mg/day, <i>or</i> Go to next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<b>SEs are intolerable</b>	Go to the next level.

Return to clinic:

Return in 3 weeks.

**CDP, Week 12****STAR★D Levels 2 - 2A - 3 - VenlafaxineXR****Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Continue current dose and go to follow-up <sup>1</sup> , <i>or</i> Go to the next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose and go to follow-up.
<b>SEs are intolerable</b>	Go to the next level.

Return to clinic:

If remitted,  
• Return in 3 months or as needed.  
If starting new level  
• Return in 2 weeks.

<sup>1</sup> Because of the severity of some patients, clinicians may choose to keep patient on current dose and move to follow-up if at week 12 the patient has maintained a score of 6-8 on the QIDS-C or if the patient does not want to change medications and/or the patient is satisfied with the level of improvement.



## Level 2 - Medication Augmentation Bupirone

<b>CDP, Week 0</b>	<b>STAR★D Level 2- Citalopram + Bupirone</b>
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Start patient on bupirone 15 mg/day in addition to current dose of citalopram for 1 week, then 30 mg/day

Return to clinic: Return in 2 weeks.

<b>CDP, Week 4</b>	<b>STAR★D Level 2- Citalopram + Bupirone</b>
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*Symptom Improvement (SEs tolerable)*

QIDS-C <sub>16</sub> ≥ 9	Increase dose to 45 mg/day.
QIDS-C <sub>16</sub> = 6-8	Continue current dose, <i>or</i> Increase dose to 45 mg/day.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<i>Improved, but SEs are intolerable</i>	Continue current dose and address SEs, <i>or</i> Go to the next level.
<i>Not improved and SEs are intolerable</i>	Go to the next level.

Return to clinic: Return in 2 weeks.

<b>CDP, Week 6</b>	<b>STAR★D Level 2- Citalopram + Bupirone</b>
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*Symptom Improvement (SEs tolerable):*

QIDS-C <sub>16</sub> ≥ 9	Increase dose to 60 mg/day.
QIDS-C <sub>16</sub> = 6-8	Increase dose to 60 mg/day, <i>or</i> Continue current dose.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<i>Improved, but SEs are intolerable</i>	Continue current dose and address SEs, <i>or</i> Decrease dose and continue for 2 additional weeks, <i>or</i> Go to the next level.
<i>Not improved and SEs are intolerable</i>	Go to the next level.

Return to clinic: Return in 3 weeks.

**CDP, Week 9****STAR★D Level 2- Citalopram + Buspirone****Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Increase dose to 60 mg/day if not previously done, <i>or</i> Go to next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<b>SEs are intolerable</b>	Go to the next level.

Return to clinic:

Return in 3 weeks.

**CDP, Week 12****STAR★D Level 2- Citalopram + Buspirone****Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Continue current dose and go to follow-up, <sup>1</sup> <i>or</i> Go to the next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose and go to follow-up.
<b>SEs are intolerable</b>	Go to the next level.

Return to clinic:

If remitted,  
• Return in 3 months or as needed.  
If starting new level  
• Return in 2 weeks.

<sup>1</sup> Because of the severity of some patients, clinicians may choose to keep patient on current dose and move to follow-up if at week 12 the patient has maintained a score of 6-8 on the QIDS-C or if the patient does not want to change medications and/or the patient is satisfied with the level of improvement.



## Level 2 - Medication Augmentation Bupropion SR

<b>CDP, Week 0</b>	<b>STAR★D Level 2- Citalopram + Bupropion SR</b>
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Start patient on bupropion 200 mg/day in addition to current dose of citalopram

Return to clinic: Return in 2 weeks.

<b>CDP, Week 4</b>	<b>STAR★D Level 2- Citalopram + Bupropion SR</b>
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*Symptom Improvement (SEs tolerable)*

QIDS-C <sub>16</sub> ≥ 9	Increase dose to 300 mg/day.
QIDS-C <sub>16</sub> = 6-8	Continue current dose, <i>or</i> Increase dose to 300 mg/day.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<i>Improved, but SEs are intolerable</i>	Continue current dose and address SEs, <i>or</i> Go to the next level.
<i>Not improved and SEs are intolerable</i>	Go to the next level.

Return to clinic: Return in 2 weeks.

<b>CDP, Week 6</b>	<b>STAR★D Level 2- Citalopram + Bupropion SR</b>
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*Symptom Improvement (SEs tolerable):*

QIDS-C <sub>16</sub> ≥ 9	Increase dose to 400 mg/day.
QIDS-C <sub>16</sub> = 6-8	Increase dose to 400 mg/day, <i>or</i> Continue current dose.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<i>Improved, but SEs are intolerable</i>	Continue current dose and address SEs, <i>or</i> Decrease dose and continue for 2 additional weeks, <i>or</i> Go to the next level.
<i>Not improved and SEs are intolerable</i>	Go to the next level.

Return to clinic: Return in 3 weeks.

**CDP, Week 9****STAR★D Level 2- Citalopram + Bupropion SR****Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Increase dose to 400 mg/day if not previously done, <i>or</i> Go to next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<b>SEs are intolerable</b>	Go to the next level.

Return to clinic:

Return in 3 weeks.

**CDP, Week 12****STAR★D Level 2- Citalopram + Bupropion SR****Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Continue current dose and go to follow-up, <sup>1</sup> <i>or</i> Go to the next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose and go to follow-up.
<b>SEs are intolerable</b>	Go to the next level.

Return to clinic:

If remitted,  
• Return in 3 months or as needed.  
If starting new level  
• Return in 2 weeks.

<sup>1</sup> Because of the severity of some patients, clinicians may choose to keep patient on current dose and move to follow-up if at week 12 the patient has maintained a score of 6-8 on the QIDS-C or if the patient does not want to change medications and/or the patient is satisfied with the level of improvement.



### Level 3 - Medication Switch Mirtazapine

<b>CDP, Week 0</b>	<b>STAR★D Level 3 - Mirtazapine</b>
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Start patient on mirtazapine 15 mg/day for 1 week, then 30 mg/day

Return to clinic: Return in 2 weeks.

<b>CDP, Week 4</b>	<b>STAR★D Level 3 - Mirtazapine</b>
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*Symptom Improvement (SEs tolerable)*

QIDS-C <sub>16</sub> ≥ 9	Increase dose to 45 mg/day.
QIDS-C <sub>16</sub> = 6-8	Continue current dose, <i>or</i> Increase dose to 45 mg/day.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<i>Improved, but SEs are intolerable</i>	Continue current dose and address SEs, <i>or</i> Go to the next level.
<i>Not improved and SEs are intolerable</i>	Go to the next level.

Return to clinic: Return in 2 weeks.

<b>CDP, Week 6</b>	<b>STAR★D Level 3 - Mirtazapine</b>
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*Symptom Improvement (SEs tolerable):*

QIDS-C <sub>16</sub> ≥ 9	Increase dose to 60 mg/day.
QIDS-C <sub>16</sub> = 6-8	Increase dose to 60 mg/day, <i>or</i> Continue current dose.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<i>Improved, but SEs are intolerable</i>	Continue current dose and address SEs, <i>or</i> Decrease dose and continue for 2 additional weeks, <i>or</i> Go to the next level.
<i>Not improved and SEs are intolerable</i>	Go to the next level.

Return to clinic: Return in 3 weeks.

**CDP, Week 9****STAR☆D Level 3- Mirtazapine****Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Continue current dose, <i>or</i> Increase dose to 60 mg/day, if not previously done <i>or</i> Go to next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<b>SEs are intolerable</b>	Go to the next level.

Return to clinic:

Return in 3 weeks.

**CDP, Week 12****STAR☆D Level 3 - Mirtazapine****Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Continue current dose and go to follow-up, <sup>1</sup> <i>or</i> Go to the next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose and go to follow-up.
<b>SEs are intolerable</b>	Go to the next level.

Return to clinic:

If remitted,  
• Return in 3 months or as needed.  
If starting new level  
• Return in 2 weeks.

<sup>1</sup> Because of the severity of some patients, clinicians may choose to keep patient on current dose and move to follow-up if at week 12 the patient has maintained a score of 6-8 on the 16-item QIDS-C or if the patient does not want to change medications and/or the patient is satisfied with the level of improvement.



### Level 3- Medication Switch Nortriptyline

<b>CDP, Week 0</b>	<b>STAR★D Level 3 - Nortriptyline</b>
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Start patient on nortriptyline 25 mg/day for 3 days, 50 mg for 4 days then 75 mg/day

Return to clinic: Return in 2 weeks.

<b>CDP, Week 4</b>	<b>STAR★D Level 3 - Nortriptyline</b>
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*Symptom Improvement (SEs tolerable)*

QIDS-C <sub>16</sub> ≥ 9	Increase dose to 100 mg/day.
QIDS-C <sub>16</sub> = 6-8	Continue current dose, <i>or</i> Increase dose to 100 mg/day.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<i>Improved, but SEs are intolerable</i>	Continue current dose and address SEs, <i>or</i> Go to the next level.
<i>Not improved and SEs are intolerable</i>	Go to the next level.

Return to clinic: Return in 2 weeks.

<b>CDP, Week 6</b>	<b>STAR★D Level 3 - Nortriptyline</b>
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*Symptom Improvement (SEs tolerable):*

QIDS-C <sub>16</sub> ≥ 9	Increase dose to 150 mg/day.
QIDS-C <sub>16</sub> = 6-8	Increase dose to 150 mg/day, <i>or</i> Continue current dose.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<i>Improved, but SEs are intolerable</i>	Continue current dose and address SEs, <i>or</i> Decrease dose and continue for 2 additional weeks, <i>or</i> Go to the next level.
<i>Not improved and SEs are intolerable</i>	Go to the next level.

Return to clinic: Return in 3 weeks.

**CDP, Week 9****STAR★D Level 3- Nortriptyline****Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Continue current dose, <i>or</i> Increase dose to 150 mg/day, if not previously done <i>or</i> Go to next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<b>SEs are intolerable</b>	Go to the next level.

Return to clinic:

Return in 3 weeks.

**CDP, Week 12****STAR★D Level 3 - Nortriptyline****Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Continue current dose and go to follow-up <sup>1</sup> , <i>or</i> Go to the next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose and go to follow-up.
<b>SEs are intolerable</b>	Go to the next level.

Return to clinic:

If remitted,  
• Return in 3 months or as needed.  
If starting new level  
• Return in 2 weeks.

<sup>1</sup> Because of the severity of some patients, clinicians may choose to keep patient on current dose and move to follow-up if at week 12 the patient has maintained a score of 6-8 on the 16-item QIDS-C or if the patient does not want to change medications and/or the patient is satisfied with the level of improvement.



### Level 3 - Medication Augmentation Lithium

<b>CDP, Week 0</b>	<b>STAR★D Level 3 – Lithium</b>
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Start patient on lithium 450 mg/day for 2 weeks, Continue current dose of existing antidepressant  
(If necessary, dose may be titrated to 450 mg/day by starting patient on 225 mg/day for 1 week, then increase to 450 mg/day)

Return to clinic: Return in 2 weeks.

<b>Week 2</b>	<b>STAR★D Level 3 - Lithium</b>
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Increase dose to 900 mg/day for 1 week, then increase dose to 1350 mg/day

Return to clinic: Return in 2 weeks.

<b>CDP, Week 4</b>	<b>STAR★D Level 3 –Lithium</b>
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***Symptom Improvement (SEs tolerable)***

QIDS-C <sub>16</sub> ≥ 9	Titrate dose to maintain blood level of 0.6-1.2mEq/L.
QIDS-C <sub>16</sub> = 6-8	Titrate dose to maintain blood level of 0.6-1.2mEq/L.
QIDS-C <sub>16</sub> ≤ 5	Titrate dose to maintain blood level of 0.6-1.2mEq/L.
<b><i>Improved, but SEs are intolerable</i></b>	Titrate dose to maintain blood level of 0.6-1.2mEq/L and address SEs, <i>or</i> Go to the next level.
<b><i>Not improved and SEs are intolerable</i></b>	Go to the next level.

Return to clinic: Return in 2 weeks.



**CDP, Week 6**

**STAR★D Level 3 –Lithium**

***Symptom Improvement (SEs tolerable):***

QIDS-C <sub>16</sub> ≥ 9	Titrate dose to maintain blood level of 0.6-1.2mEq/L.
QIDS-C <sub>16</sub> = 6-8	Titrate dose to maintain blood level of 0.6-1.2mEq/L.
QIDS-C <sub>16</sub> ≤ 5	Titrate dose to maintain blood level of 0.6-1.2mEq/L.
<b><i>Improved, but SEs are intolerable</i></b>	Titrate dose to maintain blood level of 0.6-1.2mEq/L and address SEs, <i>or</i> Decrease dose and continue for 2 additional weeks, <i>or</i> Go to the next level.
<b><i>Not improved and SEs are intolerable</i></b>	Go to the next level.

Return to clinic:

Return in 3 weeks.

**CDP, Week 9**

**STAR★D Level 3 –Lithium**

***Symptom Improvement (SEs tolerable):***

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Titrate dose to maintain blood level of 0.6-1.2mEq/L <i>or</i> Go to next level.
QIDS-C <sub>16</sub> ≤ 5	Titrate dose to maintain blood level of 0.6-1.2mEq/L..
<b><i>SEs are intolerable</i></b>	Go to the next level.

Return to clinic:

Return in 3 weeks.

**CDP, Week 12**

**STAR★D Level 3 –Lithium**

***Symptom Improvement (SEs tolerable):***

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Titrate dose to maintain blood level of 0.6-1.2mEq/L and go to follow-up <sup>1</sup> , <i>or</i> Go to the next level.
QIDS-C <sub>16</sub> ≤ 5	Titrate dose to maintain blood level of 0.6-1.2mEq/L and go to follow-up.
<b><i>SEs are intolerable</i></b>	Go to the next level.

Return to clinic:

If remitted,  

- Return in 3 months or as needed.

 If starting new level  

- Return in 2 weeks.



<sup>1</sup> Because of the severity of some patients, clinicians may choose to keep patient on current dose and move to follow-up if at week 12 the patient has maintained a score of 6-8 on the 16-item QIDS-C or if the patient does not want to change medications and/or the patient is satisfied with the level of improvement.





### Level 3 - Medication Augmentation T<sub>3</sub>

**CDP, Week 0** **STAR★D Level 3 – T<sub>3</sub>**

Start patient on T<sub>3</sub> 25 µg/day for 1 week, then 50 µg/day.  
Continue current dose of existing antidepressant

Return to clinic: Return in 2 weeks.

**CDP, Week 4** **STAR★D Level 3 –T<sub>3</sub>**

***Symptom Improvement (SEs tolerable)***

QIDS-C <sub>16</sub> ≥ 9	Continue current dose.
QIDS-C <sub>16</sub> = 6-8	Continue current dose.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<b><i>Improved, but SEs are intolerable</i></b>	Continue current dose and address SEs, <i>or</i> Go to the next level.
<b><i>Not improved and SEs are intolerable</i></b>	Go to the next level.

Return to clinic: Return in 2 weeks.

**CDP, Week 6** **STAR★D Level 3 – T<sub>3</sub>**

***Symptom Improvement (SEs tolerable):***

QIDS-C <sub>16</sub> ≥ 9	Continue current dose <i>or</i> Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Continue current dose <i>or</i> Go to the next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<b><i>Improved, but SEs are intolerable</i></b>	Continue current dose and address SEs, <i>or</i> Decrease dose and continue for 2 additional weeks, <i>or</i> Go to the next level.
<b><i>Not improved and SEs are intolerable</i></b>	Go to the next level.

Return to clinic: Return in 3 weeks.

**CDP, Week 9****STAR★D Level 3 – T<sub>3</sub>****Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Continue current dose, <i>or</i> Go to next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<b>SEs are intolerable</b>	Go to the next level.

Return to clinic:

Return in 3 weeks.

**CDP, Week 12****STAR★D Level 3 – T<sub>3</sub>****Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Continue current dose and go to follow-up, <sup>1</sup> <i>or</i> Go to the next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose and go to follow-up.
<b>SEs are intolerable</b>	Go to the next level.

Return to clinic:

If remitted,  
• Return in 3 months or as needed.  
If starting new level  
• Return in 2 weeks.

<sup>1</sup> Because of the severity of some patients, clinicians may choose to keep patient on current dose and move to follow-up if at week 12 the patient has maintained a score of 6-8 on the 16-item QIDS-C or if the patient does not want to change medications and/or the patient is satisfied with the level of improvement.



## **Level 4**

Upon entry to Level 4, the clinician will discuss with the patient the options available at this level to determine patient acceptability. The patient will then be randomized to one option that is deemed acceptable and medically safe. Refer to the appropriate treatment table for each option. If the patient has been treated by a Primary Care clinician during Levels 1, 2 and 3, and it is determined that the patient should be treated at a Specialty Clinic for Level 4, the following steps are to be taken:

- a. Randomize the patient at the time the determination is made to go to Level 4.
- b. Have the patient seen at the Specialty Clinic within 2 days, OR
- c. Prescribe the Level 4 medication and the Regional Director or Associate Director will assume the patient's care until they are seen at the Specialty Clinic.

The patient must know at all times who his treating clinician is and how to contact him.

### **Level 4 Treatment Strategies/Options**

- Tranylcypromine (TCP), see page 0
- Mirtazapine + Venlafaxine (MIRT + VEN), see page 0

### **Level 4 - Medication Switch Tranylcypromine**

**CDP, Week 0**

**STAR★D Level 4 - Tranylcypromine**

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**Start patient on tranylcypromine 10 mg/day**

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Return to clinic:

Return in 2 weeks.

**Week 2**

**STAR★D Level 4 - Tranylcypromine**

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**Increase dose to 30 mg/day for 1 week, then 40 mg/day**

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Return to clinic:

Return in 2 weeks.

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**CDP, Week 4****STAR★D Level 4 - Tranylcypromine*****Symptom Improvement (SEs tolerable)***

QIDS-C <sub>16</sub> ≥ 9	Increase dose to 50 mg/day.
QIDS-C <sub>16</sub> = 6-8	Continue current dose, <i>or</i> Increase dose to 50 mg/day.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<b><i>Improved, but SEs are intolerable</i></b>	Continue current dose and address SEs, <i>or</i> Go to the next level.
<b><i>Not improved and SEs are intolerable</i></b>	Go to the next level.

Return to clinic:

Return in 2 weeks.

**CDP, Week 6****STAR★D Level 4 - Tranylcypromine*****Symptom Improvement (SEs tolerable):***

QIDS-C <sub>16</sub> ≥ 9	Increase dose to 60 mg/day.
QIDS-C <sub>16</sub> = 6-8	Increase dose to 60 mg/day, <i>or</i> Continue current dose.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<b><i>Improved, but SEs are intolerable</i></b>	Continue current dose and address SEs, <i>or</i> Decrease dose and continue for 2 additional weeks, <i>or</i> Go to the next level.
<b><i>Not improved and SEs are intolerable</i></b>	Go to the next level.

Return to clinic:

Return in 3 weeks.

**CDP, Week 9****STAR★D Level 4 - Tranylcypromine*****Symptom Improvement (SEs tolerable):***

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Continue current dose, <i>or</i> Increase dose to 60 mg/day, if not previously done <i>or</i> Go to next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<b><i>SEs are intolerable</i></b>	Go to the next level.

Return to clinic:

Return in 3 weeks.



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**CDP, Week 12****STAR★D Level 4 - Tranylcypromine*****Symptom Improvement (SEs tolerable):***

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Continue current dose and go to follow-up, <sup>1</sup> <i>or</i> Go to the next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose and go to follow-up.
<b><i>SEs are intolerable</i></b>	Go to the next level.
Return to clinic:	If remitted, • Return in 3 months or as needed. If starting new level • Return in 2 weeks.

<sup>1</sup> Because of the severity of some patients, clinicians may choose to keep patient on current dose and move to follow-up if at week 12 the patient has maintained a score of 6-8 on the 16-item QIDS-C or if the patient does not want to change medications and/or the patient is satisfied with the level of improvement.





## Level 4 - Medication Switch Mirtazapine + Venlafaxine XR

**CDP, Week 0**

**STAR★D Level 4 – Mirtazapine + Venlafaxine XR**

Start patient on venlafaxineXR 37.5 for 7 days, then 75 mg/day for 7days, then 150 mg/day and mirtazapine 15 mg/q h.s.

Return to clinic:

Return in 2 weeks.

**Week 2**

**STAR★D Level 4 - Mirtazapine + Venlafaxine XR**

Increase venlafaxine dose to 150 mg/q a.m. and continue mirtazapine dose

Return to clinic:

Return in 2 weeks.

**CDP, Week 4**

**STAR★D Level 4 - Mirtazapine + Venlafaxine XR**

***Symptom Improvement (SEs tolerable)***

QIDS-C<sub>16</sub> ≥ 9

Increase mirtazapine dose to 30 mg/q h.s. and Continue venlafaxine dose.

QIDS-C<sub>16</sub> = 6-8

Continue current dose, *or* Increase mirtazapine dose to 30 mg/q h.s. and Continue venlafaxine dose.

QIDS-C<sub>16</sub> ≤ 5

Continue current dose.

***Improved, but SEs are intolerable***

Continue current dose and address SEs, *or* Go to the next level.

***Not improved and SEs are intolerable***

Go to the next level.

Return to clinic:

Return in 2 weeks.

**CDP, Week 6****STAR★D Level 4 - Mirtazapine + Venlafaxine XR****Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Increase venlafaxine dose to 225 mg/q a.m. and Continue mirtazapine dose.
QIDS-C <sub>16</sub> = 6-8	Increase venlafaxine dose to 225 mg/q a.m. and Continue mirtazapine dose, <i>or</i> Continue current dose.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<b>Improved, but SEs are intolerable</b>	Continue current dose and address SEs, <i>or</i> Decrease dose and continue for 2 additional weeks, <i>or</i> Go to the next level.
<b>Not improved and SEs are intolerable</b>	Go to the next level.

Return to clinic:

Return in 3 weeks.

**CDP, Week 9****STAR★D Level 4 - Mirtazapine + Venlafaxine XR****Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Continue current dose, <i>or</i> Increase venlafaxine dose to 225 mg/q a.m. if not previously done and Continue mirtazapine dose, <i>or</i> Increase venlafaxine dose to 300 mg/q a.m., and Continue mirtazapine dose <i>or</i> Go to next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose.
<b>SEs are intolerable</b>	Go to the next level.

Return to clinic:

Return in 3 weeks.



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**CDP, Week 12****STAR★D Level 4 - Mirtazapine + Venlafaxine XR****Symptom Improvement (SEs tolerable):**

QIDS-C <sub>16</sub> ≥ 9	Go to the next level.
QIDS-C <sub>16</sub> = 6-8	Increase mirtazapine dose to 45 mg/q h.s. and Continue venlafaxine dose, <i>or</i> Continue current dose and go to follow-up, <sup>1</sup> <i>or</i> Go to the next level.
QIDS-C <sub>16</sub> ≤ 5	Continue current dose and go to follow-up.
<b>SEs are intolerable</b>	Go to the next level.
Return to clinic:	If remitted, • Return in 3 months or as needed. If starting new level • Return in 2 weeks.

<sup>1</sup> Because of the severity of some patients, clinicians may choose to keep patient on current dose and move to follow-up if at week 12 the patient has maintained a score of 6-8 on the 16-item QIDS-C or if the patient does not want to change medications and/or the patient is satisfied with the level of improvement.



# Clinical Procedures Manual

Overview of STAR★D	Levels of Treatment	STAR★D At A Glance Table	Inclusion/Exclusion Criteria	General Principles	Treatment Implementation
	<b>Medication Dosing Table</b>	Side Effects/ Adverse Events	Clinical Research Coordinator	Data Management & Collection	Appendix

## Medication Dosing Table

Details about initial dosing can be found in Appendix C.

**Table 1: Medication Dosing Used for the Treatment of Depression**

Type/ Class	Medication	Minimum Therapeutic Dose (Level)	Maximum Dose (Level)	Recommended Administration Schedule
SSRI	Sertraline (Zoloft)	100 mg	200 mg	QAM
	Citalopram (Celexa)	20 mg	60 mg	QAM
TCA	Nortriptyline (Pamelor)	50 mg	150 mg (100-150ng/L)	QHS
Others	Bupropion SR (Wellbutrin SR)	300 mg	400 mg	BID <sub>≤</sub> 200mg/ dose BID
	Venlafaxine XR (Effexor XR)	150 mg	375 mg	QHS
	Mirtazapine (Remeron)	30 mg	60 mg	
MAOI	Tranlycypromine (Parnate)	40 mg	60 mg	QD - TID
Augmenting Agents	Bupirone (BuSpar)	30 mg	60 mg	BID-TID
	Lithium	0.6-0.8 mEq/L	1.0 -1.2mEq/L	BID
	T <sub>3</sub>	25-50 mcg	50 mcg	QAM

<sup>1</sup> If the patient experiences intolerable side effects after the initial dose or subsequent dose adjustments, the dosage may be decreased or timing of administration can be changed.



# Clinical Procedures Manual

Overview of STAR★D	Levels of Treatment	STAR★D At A Glance Table	Inclusion/Exclusion Criteria	General Principles	Treatment Implementation
	Medication Dosing Table	<b>Side Effects/ Adverse Events</b>	Clinical Research Coordinator	Data Management & Collection	Appendix

## Side Effects Table

Table 2: Side Effects (SEs) for Protocol Medications

MEDICATION	SIDE EFFECTS
<b>Citalopram</b> <b>Sertraline</b>	<ul style="list-style-type: none"> <li>Dizziness, dry mouth, insomnia, agitation, nausea, sexual dysfunction, headache</li> </ul>
<b>Bupropion SR</b>	<ul style="list-style-type: none"> <li>Headache, agitation, weight loss, insomnia, nausea</li> </ul>
<b>Venlafaxine XR</b>	<ul style="list-style-type: none"> <li>Dizziness, somnolence, insomnia, decreased appetite, anxiety, headache, nausea, hypertension</li> </ul>
<b>Nortriptyline</b>	<ul style="list-style-type: none"> <li>Sedation, dizziness, dry mouth, nausea, insomnia, anxiety, anticholinergic effects</li> </ul>
<b>Mirtazapine</b>	<ul style="list-style-type: none"> <li>Dizziness, diarrhea, increased appetite, drowsiness, dry mouth</li> </ul>
<b>Tranlycypromine</b>	<ul style="list-style-type: none"> <li>Restlessness, dizziness, blurred vision, diarrhea, insomnia, weakness, hypotension</li> </ul>
<b>Buspirone</b>	<ul style="list-style-type: none"> <li>Dizziness, nausea/vomiting, insomnia, dry mouth, nervousness</li> </ul>
<b>T<sub>3</sub></b>	<ul style="list-style-type: none"> <li>Insomnia, diarrhea, tremor, increased/decreased appetite, headache, heat intolerance, nausea</li> </ul>
<b>Lithium</b>	<ul style="list-style-type: none"> <li>Fainting, tremor, drowsiness, muscle weakness, nausea/vomiting, thirst</li> </ul>



## Guidelines for Beginning Antidepressant Therapy and Dosing<sup>1</sup>

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**Citalopram:** An SSRI which is a very effective inhibitor on neuronal serotonin reuptake. Absorption is fast, almost complete, and unaffected by food. Bio-availability is 80% with a half-life of 35 hours. Citalopram is 80% protein bound with a low potential for interaction with drugs metabolized by the CYP2D6 system. Should not be used with MAOIs. Much less cardiotoxic than tricyclic and tetracyclic antidepressants.

### **Dosing**

- Initial dose 20 mg
- Minimum therapeutic dose is 20-40 mg
- Maximum dose is 60 mg
- Maximum dose for patients >65 years of age is 40 mg qd
- Half-life is 35 hours

### **Side Effects**

- dizziness
- headache
- sleep disturbances
- dry mouth
- nausea

**Sertraline:** An SSRI which inhibits serotonin reuptake in the CNS, increases action of serotonin but does not affect dopamine or norepinephrine. Uses include major depression and obsessive-compulsive disorder. Sertraline peaks in 5–9 hours reaching a steady state in 1 week. It is 99% plasma protein binding with a half-life of 1–4 days. It is also extensively metabolized and excreted in urine. May cause fatal reactions when used in combination with MAOIs. May also cause altered lithium levels when combined with lithium. Taking with food decreases the time required to reach peak plasma levels.

### **Dosing**

- Initial dose 50 mg q am
- Minimum therapeutic dose 100 -150 mg
- Maximum dose 200 mg

### **Side Effects**

- headache
- insomnia
- agitation
- nausea
- diarrhea
- sexual dysfunction

**Bupropion SR:** An antidepressant that inhibits the reuptake of dopamine, serotonin and norepinephrine. Uses include major depression and smoking cessation. Onset of medication is 2–4 weeks with a half-life of 12–14 hours. Bupropion is metabolized by the liver and reaches a steady state in 1 week. Contraindicated in seizure disorder and eating disorders. Use cautiously in patients with renal and hepatic disease, recent MI or cranial trauma.

### **Dosing**

- Initial dose 150 mg/d
- Minimum therapeutic dose 150 mg bid
- Maximum dose is 200 mg bid
- Half-life is 21 hours.
- Do not give to patients with history of seizures

### **Side Effects**

- headache
- restlessness
- insomnia
- agitation
- nausea
- weight loss
- decreased libido



**Venlafaxine XR:** Potent inhibitor of neuronal serotonin and norepinephrine uptake and a weak inhibitor of dopamine. Extensively metabolized in the liver to an active metabolite with 87% of drug recovered in the urine. 27% protein binding with a half-life of 48 hours. May cause hyperthermia, rigidity, rapid fluctuations of vital signs and mental status changes when used with MAOIs. Use cautiously in patients with mania, hypertension or seizure disorder.

<b>Dosing</b>	<b>Side Effects</b>
<ul style="list-style-type: none"><li>• Initial dose is 37.5 mg qd</li><li>• Minimum therapeutic dose is 75–150 mg qd</li><li>• Maximum daily dose is 375 mg qd</li><li>• Use with caution in patients with hypertension and monitor blood pressure</li><li>• Half-life is 48 hours</li></ul>	<ul style="list-style-type: none"><li>• dizziness</li><li>• anxiety</li><li>• somnolence</li><li>• headache</li><li>• insomnia</li><li>• nausea</li><li>• decreased appetite</li><li>• hypertension</li></ul>

**Nortriptyline:** Tricyclic antidepressant that blocks the reuptake of norepinephrine and serotonin into nerve endings, increasing the action of norepinephrine and serotonin in nerve cells. Contraindicated in the recovery phase of myocardial infarctions, convulsive disorders and prostatic hypertrophy. Increases effects of epinephrine, alcohol, barbiturates, benzodiazepines and CNS depressants. Possible hyperpyretic crisis, convulsions or hypertensive episode may occur if used with MAOIs. Do not break, crush or chew.

<b>Dosing</b>	<b>Side Effects</b>
<ul style="list-style-type: none"><li>• Initial dose is 25 mg qhs</li><li>• Minimum therapeutic dose is 75–100 mg.</li><li>• Maximum daily dose is 150 mg qhs</li><li>• Effective plasma levels for this medication are 50–150 ng/ml.</li><li>• Half-life is 18–44 hours</li></ul>	<ul style="list-style-type: none"><li>• sedation</li><li>• anticholinergic effects</li><li>• dizziness</li><li>• anxiety</li><li>• dry mouth</li><li>• insomnia</li><li>• nausea</li></ul>

**Mirtazapine:** Tetracyclic antidepressant that blocks the reuptake of norepinephrine and serotonin into nerve endings, increasing the action of norepinephrine and serotonin in nerve cells. Contraindicated in the recovery phase of myocardial infarctions, convulsive disorders and prostatic hypertrophy. Increases effects of epinephrine, alcohol, barbiturates, benzodiazepines and CNS depressants. Possible hyperpyretic crisis, convulsions or hypertensive episode may occur if used with MAOIs.

<b>Dosing</b>	<b>Side Effects</b>
<ul style="list-style-type: none"><li>• Initial dose is 15 mg qhs</li><li>• Minimum therapeutic dose is 30 mg qd</li><li>• Maximum dose is 60 mg</li><li>• Half-life is 20–40 hours</li></ul>	<ul style="list-style-type: none"><li>• dizziness</li><li>• drowsiness</li><li>• diarrhea</li><li>• dry mouth</li><li>• increased appetite</li></ul>



**Tranlycypromine:** MAOI antidepressant that increases concentrations of endogenous epinephrine, norepinephrine, serotonin, and dopamine in storage sites in the central nervous system by inhibiting MAO. Increased concentrations reduce depression. Contraindicated in hypertension, elderly, CHF, severe hepatic disease, pheochromocytoma, severe renal disease and severe cardiac disease. Increases hypotension when given with thiazide diuretics. Possible toxicity when given with sumatriptan, sulfonamide. Increased hypoglycemic effect with antidiabetics.

### **Dosing**

- Initial dose is 10 mg qd in divided doses
- Minimum therapeutic dose is 30 mg qd in divided doses
- Target dose is 60 mg qd
- Caution patients to avoid tyramine-rich foods and drug interactions such as epinephrine, amphetamines, dopamine, etc. Hypertensive crisis can occur.

### **Side Effects**

- restlessness
- insomnia
- dizziness
- weakness
- blurred vision
- arrhythmias
- diarrhea
- hypotension



## ***Guidelines for Augmentation Therapy and Dosing***

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**Lithium**: Antimanic which may alter sodium, potassium ion transport across cell membrane in nerve or muscle cells and may balance biogenic amines of norepinephrine and serotonin in CNS areas involved in emotional responses. Contraindicated in hepatic disease, renal disease, brain trauma, and severe cardiac or renal disease. Increased toxicity with indomethacin, diuretics, nonsteroidal antiinflammatories.

### **Dosing**

- Initial dose for augmentation is 450 mg/day and should be adjusted to reach plasma level of 0.6–1.2 mEq/L
- May start on 225 mg/day for 1 week, then 450 mg/day.

### **Side Effects at Therapeutic Blood Level**

- fainting
- drowsiness
- nausea/vomiting
- tremor
- muscle weakness
- thirst

**Buspirone**: Antianxiety agent that acts by inhibiting the action of serotonin. May also be used in augmentation therapy due to increased effects when used with psychotropic drugs. Use cautiously in elderly patients and patients with impaired hepatic/renal functioning. Increased ALT when combined with trazodone. Do not use with MAOIs.

### **Dosing**

- Initial dose is 15 mg/d
- Maximum dose is 60 mg/d

### **Side Effects**

- dizziness
- insomnia
- nervousness
- nausea/vomiting
- dry mouth

**Liothyronine (T<sub>3</sub>)**: Increases metabolic rates, cardiac output, oxygen consumption, body temperature, blood volume, growth, and development at the cellular level. Use cautiously in elderly patients and patients with angina pectoris, hypertension, ischemia, cardiac disease, pregnancy, and lactation. Increases the effects of TCAs, as well as anticoagulants and sympathomimetics. Decreases the effects of digitalis drugs, insulin, hypoglycemics, liothyronine, and estrogens.

### **Dosing**

- Initial dose is 25 mcg qd, increased by 12.5–25 mcg q 1–2 weeks until desired response.
- Maintenance dose is 50 mcg qd.

### **Side Effects**

- headache
- insomnia
- nausea
- tremor
- diarrhea
- increased/decreased appetite



## ***Guidelines for Adequate Treatment Trials of Antidepressants***

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Please use the following as a guideline to determine adequate trials for antidepressant medications used in the protocol.

<b>MEDICATION</b>	<b>DOSAGE (TOTAL DAILY DOSE)</b>	<b>DURATION</b>
Citalopram	40 mg	6 weeks
Sertraline	150 mg	6 weeks
BupropionSR	300 mg	6 weeks
Fluoxetine	40 mg	6 weeks
Paroxetine	40 mg	6 weeks
VenlafaxineXR	225 mg	6 weeks
Mirtazapine	30 mg	6 weeks
Nortriptyline	100 mg	6 weeks
Tranlycypromine	40 mg	6 weeks
Fluvoxamine	200 mg	6 weeks

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### ***Rules for tapering medications:***

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In Levels 1-4 (**except MAOIs**), the clinician may choose to either:

- ★ Discontinue medication #1 and immediately begin medication #2

Or

- ★ Decrease medication #1 to initiate medication #2 at low dose and taper/titrate over 1 week

### ***Rules for switching to a MAOI***

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When switching to a MAOI, the clinician may choose to either:

- ★ Discontinue medication #1 and immediately start the 7 – 10 day washout period before initiating the MAOI

Or

- ★ Gradually decrease dose of medication #1 before beginning the 7-10 day washout period prior to initiating the MAOI

**THERE MUST BE A 7-10 DAY WASHOUT PERIOD BETWEEN LEVEL 3 MEDICATION(S) AND MAOI.**



## **Adverse Events**

Medication side effects or adverse events can range from a minor annoyance to life-threatening situations. The more side effects that a patient is experiencing and the greater the daily interference that the side effects have on the patient's life, the less adherent to treatment patients are likely to be. Whether serious or not, it is important to track these side effects being experienced by each patient. In this study, side effects are assessed by self-rated questionnaires at each clinic visit and during ROA calls to the patient in follow-up.

**Serious Adverse Events (SAE)**: An SAE is defined as any event during the course of the study that:

1. Results in death,
2. Is life-threatening,
3. Is a failed suicide attempt,
4. Requires inpatient hospitalization or prolongs existing hospitalization,
5. Results in a persistent or severe disability/incapacity,
6. Is medically significant, or
7. Results in a congenital anomaly/birth defect.

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 subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

*Note: If at any time it is questionable whether an adverse event qualifies as an SAE or not, complete the SAE Checklist (See Appendix F) and/or contact the Clinical Manager.*

## **Reporting of SAEs**

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

1. Complete the SAE checklist.
2. The Serious Adverse Event form must be completed and faxed to the Data Coordinating Center (DCC) within 24 hours of the SAE being reported to the clinical site (866-748-PITT [866-748-7488]). If the patient is hospitalized, be sure to indicate the date of discharge, if applicable, and whether or not the patient is continuing in the study. As long as STAR\*<sup>®</sup>D treatment can continue, the patient can remain in the study. (Hospitalization alone is not a reason to exit a subject.)



3. The STAR★D Safety Officer, Dr. Madhukar Trivedi is available 24 hours a day/7 days a week to respond to reports of SAEs or any other safety issues (214-648-4282). Dr. Andrew Nierenberg, from the Boston Special Function Regional Center, backs up Dr. Trivedi as the STAR★D Safety Officer and also is available 24 hours a day/7 days a week (617-724-0837). The Safety Officer, with the assistance of the Clinical Manager and the Operations Manager, reports these events to the STAR★D PI and Co-PI (Drs. A. John Rush and Maurizio Fava).

Upon receipt of the SAE form the DCC will send a copy of the SAE via email to the Safety Officers, the Clinical Manager, the NIMH Program Coordinator, and if the patient is in follow-up, to the CRC.

Any SAE that is determined by the clinician to be related to a study drug and an unexpected event is to be reported to the FDA by the clinician within 15 days using the MedWatch system (<http://www.fda.gov/medwatch/report/instruct.htm>). Copies of the MedWatch report are to be sent to the Clinical Manager at the NCC and the site IRB. The NCC will notify the NIMH, the Safety Officers and the pharmaceutical company if appropriate.

4. If the SAE is continuing at the time of the initial report (e.g., the patient remains in the hospital), the CRC will send a second SAE report a week after the initial report. If the SAE is not resolved after one week, a resolution report is to be submitted as soon as the event is resolved.
5. The DCC will also send the Safety Officers a copy of the SAE Summary Form. The Safety Officer will review the SAE form and may collaborate with the clinician to determine if the SAE is a serious adverse event, if it is related to the study treatment, and if was expected following FDA guidelines. (*Unexpected adverse drug experience is any adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity.*)
6. The Safety Officer will submit the completed SAE Summary Form to the DCC within 72 hours. The DCC will distribute this information to the Regional Center Director, the CRC, the Operations Manager, the Clinical Manager, and the NIMH Program Coordinator.

### **Review of SAEs**

In addition to the submission of the study SAE Form, each Regional Center should follow their local IRB regulations and submit to them all required information. The NIMH DSMB reviews all reported SAEs quarterly. SAEs that are related to study medication and are unexpected are reviewed by the DSMB as they occur. Notices of these reviews are sent to each Regional Center to inform local IRBs of the central review.



# Clinical Procedures Manual

Overview of STAR★D	Levels of Treatment	STAR★D At A Glance Table	Inclusion/Exclusion Criteria	General Principles	Treatment Implementation
	Medication Dosing Table	Side Effects/ Adverse Events	<b>Clinical Research Coordinator</b>	Data Management & Collection	Appendix

## *Clinical Research Coordinator*

### *Overview of Clinical Research Coordinator Responsibilities/Procedures*

The Clinical Research Coordinator (CRC) plays a vital role in the implementation of the STAR★D protocol. The CRC is responsible along with the clinical site physicians for the implementation of the clinical protocol at each site. The CRC oversees all clinical visit data collection, conducts the intake interview, preliminarily monitors all patient data, ensures that each provider is adhering to the protocol, reports any deviations from the protocol, transmits all data to the Data Coordinating Center at Pittsburgh, and addresses any data queries from the Data Coordinating Center in Pittsburgh and the NCC in Dallas. (A more detailed explanation of the CRC's responsibilities is described in the STAR★D Regional Center Manual.)

Ideally, the CRC will have 1-2 designated "STAR★D days" a week at each clinical site, depending on the number of sites at the Regional Center. It will be on those days that recruitment takes place, and visits should be scheduled **accordingly**. Because each clinical site operates differently and clinician availability varies from site to site, this is only a recommendation. The goal is to optimize the CRC's time and decrease the amount of time **spent** traveling from site to site. It is the responsibility of the CRC to coordinate with the clinical site to determine the ideal operating procedures for that particular site and the Regional Center. The CRC should allow at least one day a week to be at the Regional Center to complete administrative tasks (e.g., queries, data transmission, communication with the NCC, patient follow-ups for missed visits, etc.).

### *CRC Training and Certification*

Initial training for the CRCs will take place at the Regional Center training session in Dallas. This training will include a thorough discussion of the protocol and treatment implementation. At this training session, the CRCs will also be trained in the administration of the QIDS-C<sub>16</sub>.

Immediately prior to enrolling patients at each RC, the CRC will go through a four-step **data** certification process:

1. Telephone training session.
2. Test IVR call.
3. Test forms transmission.
4. **Web-based** CRC certification exam.

The first step consists of a telephone training session involving the DCC, HTS, the Clinical Manager, and the ROA Supervisor. This is a 1½-hour training that covers the data management aspects of the study. Topics covered on this call include:



- ★ Patient ID generation
- ★ Forms generation
- ★ Forms completion
- ★ Faxing instructions
- ★ Filing suggestions
- ★ Corrections to data forms
- ★ IVR enrollment/randomization
- ★ ROA notification
- ★ Web site utilization

The second step consists of a test enrollment/randomization call to the IVR system by the CRC. Third, the CRC will complete a test **subset** of data forms and fax them to the DCC to ensure proper completion. Finally, the CRC will complete a web-based certification exam that covers various procedural aspects of the study. Once all four steps have been completed, the CRC is certified for one year.

The CRCs will be re-certified annually. The purpose of the re-certification is to ensure that the CRCs have a current knowledge of the study procedures and protocol, and any procedural changes that may have occurred during the year. The re-certification process will involve a telephone training session involving the DCC, HTS, the Clinical Manager, and the ROA Supervisor, followed by a web-based re-certification exam.

In the event a new CRC is hired, the training of that CRC will be dependent on the amount of overlap with the outgoing CRC and the outgoing CRC's ability to train the new individual. The new CRC must either be trained by the current CRC or by the Clinical Manager, and then must go through the Data Coordinating Center CRC training call and certification before being authorized to see patients.

### ***Backup CRC Training and Certification***

Each Regional Center **must** appoint one individual (or more) who will function as a backup CRC in the event that the CRC cannot meet with scheduled patients at the clinical sites. Each backup CRC must be entered into the STAR\*D Web Site directory and assigned a study identification number. Backup CRCs will participate in all the appropriate training procedures, will be certified, and will be re-certified annually.



## ***Patient Screening and Intake Procedures***

The referral/recruitment process is outlined below. See Figure 7 for a flowchart representation of the intake visit procedures.

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

### Pre-screen

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

- Patient has clinically significant depression as judged by the clinician.
- Medication is a clinically appropriate option for the treatment of depression.
- Patient is between 18 – 75.
- Patient does not have a history of psychosis, as judged by the clinician.
- Patient does not currently require hospitalization for the treatment of depression or for other medical reasons.
- Patient has no definitive prior treatment resistance history to any study medication.
- Patient does not require more treatment/care for the depression than is available in the protocol.
- Patient does not have a definitive history of lack of efficacy with SSRIs.

### Screening

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.

*Note: Ideally, referrals will take place on the specified STAR ★D day for that clinical site so that the CRC is onsite to talk to the patient. If the CRC is not available, the clinician will ask the patient to come back on the STAR ★D day.*

- ★ The CRC will assign a Study ID number per protocol (see Data Management section) and will enter the patient's name and date of screening onto the screening log.
- ★ *Note: A Study ID number will be assigned to every patient with whom the CRC has a **face-to-face** meeting for the purpose of screening.*



- ★ The CRC will begin completing a Protocol Eligibility Form, documenting demographic information in the first four items on that form.
- ★ The CRC explains the study to the patient, using the Welcome to STAR★D brochure.
- ★ If during the initial conversation with the CRC the patient indicates that he or she will not meet the inclusion or exclusion criteria, the CRC will document on the Protocol Eligibility Form the reasons the patient was not offered consent.
- ★ If the CRC determines that the patient may be eligible for the study, the CRC will obtain informed consent (see Instructions for Obtaining Informed Consent). If the patient refuses, the CRC will record the reason that the patient refused to participate in the study on page 2 of the Protocol Eligibility Form.
- ★ If the Informed Consent has been signed, the CRC will perform the baseline interview and administer the measures to determine eligibility (see below for order of administration).
  1. QIDS-C<sub>16</sub>/HRS-D<sub>17</sub> (Combined Interview).
  2. Patient Diagnostic Screening Questionnaire (self-report).
  3. Psychiatric and Medication History.
  4. CIRS (See CIRS Administration Manual, Appendix)
  5. Demographics Form (self-report).
- ★ Pages 3 and 4 of the Protocol Eligibility Form will be completed to document inclusion and exclusion criteria.
- ★ *Note: If at any time during the above assessments ineligibility is determined and/or the patient does not sign informed consent, the patient will be excluded from the study and the screening process will be terminated. The patient is referred back to the clinician for nonstudy treatment.*
- ★ If the patient is eligible, the CRC calls a toll-free number (**800-667-3315**) to register the patient via the IVR to activate the patient (see Instructions for Randomization). At this time the CRC completes the screening packet.
- ★ The CRC explains further study procedures and the importance of adherence to these procedures. Below is a list of information to be given to the patient:
  - Contact numbers **for CRC and treating clinician**.
  - Pharmacy Card information (see STAR★D Pharmacy Card).
  - IVR phone number and when to call.
  - Visit frequency and importance of keeping appointments.



- Outcomes assessment frequency.
- Importance of maintaining the blind with the Research Outcomes Assessor (ROA).

*Note: The CRC is the main contact person regarding the study and the study treatment. It should be emphasized to the patient if he/she has any questions or problems relating to the study medication to notify the CRC.*

- ★ Patient Education is initiated (see Patient Education Manual).
- ★ At this time, Level 1 treatment is started by the clinician.
- ★ The CRC faxes the CRF to the Pittsburgh DCC (**866-748-PITT [866-748-7488]**). This should be sent on the same day as the baseline visit. The remainder of the baseline packet should be faxed from the RC on the designated faxing day.
- ★ *Note: Notification to the DCC can be done at the end of the day to save time if there is more than one enrollment on that day.*
- ★ The CRC calls the STAR ★D Answering Service (**877-798-3444**) and reports the needed patient information (name, phone number, language preference, and best time and date to contact) to the ROAs to begin the baseline outcomes assessment procedures. When leaving the information on the voicemail, speak very clearly and spell out the patient's name. It is very important that the CRC does not indicate what phase the patient is in (e.g., entering follow-up, exiting, Level 2).
- ★ *Note: This information **must** be phoned in immediately after the visit, in order for the ROAs to contact the patient and obtain the baseline outcome assessment package **within the 24-hour window**. Also inform the patient of the following information:*

*ض The importance of being available within the 24-hour window.*

*ض The ROA will be calling from a remote location and cannot be called back.*

*ض The ROA will be asking information related to income.*

*Note: If for any reason the CRC can not reach the STAR ★D Answering Service, in order to meet the 24 hour deadline the patient information should be called in and left on the STAR ★D Communication Desk voicemail at 214/648-4623.*

*Note: The information that is called in to the ROA is confidential **and is not sent** to the DCC.*



Figure 7. STAR★D Screening Visit Flowchart

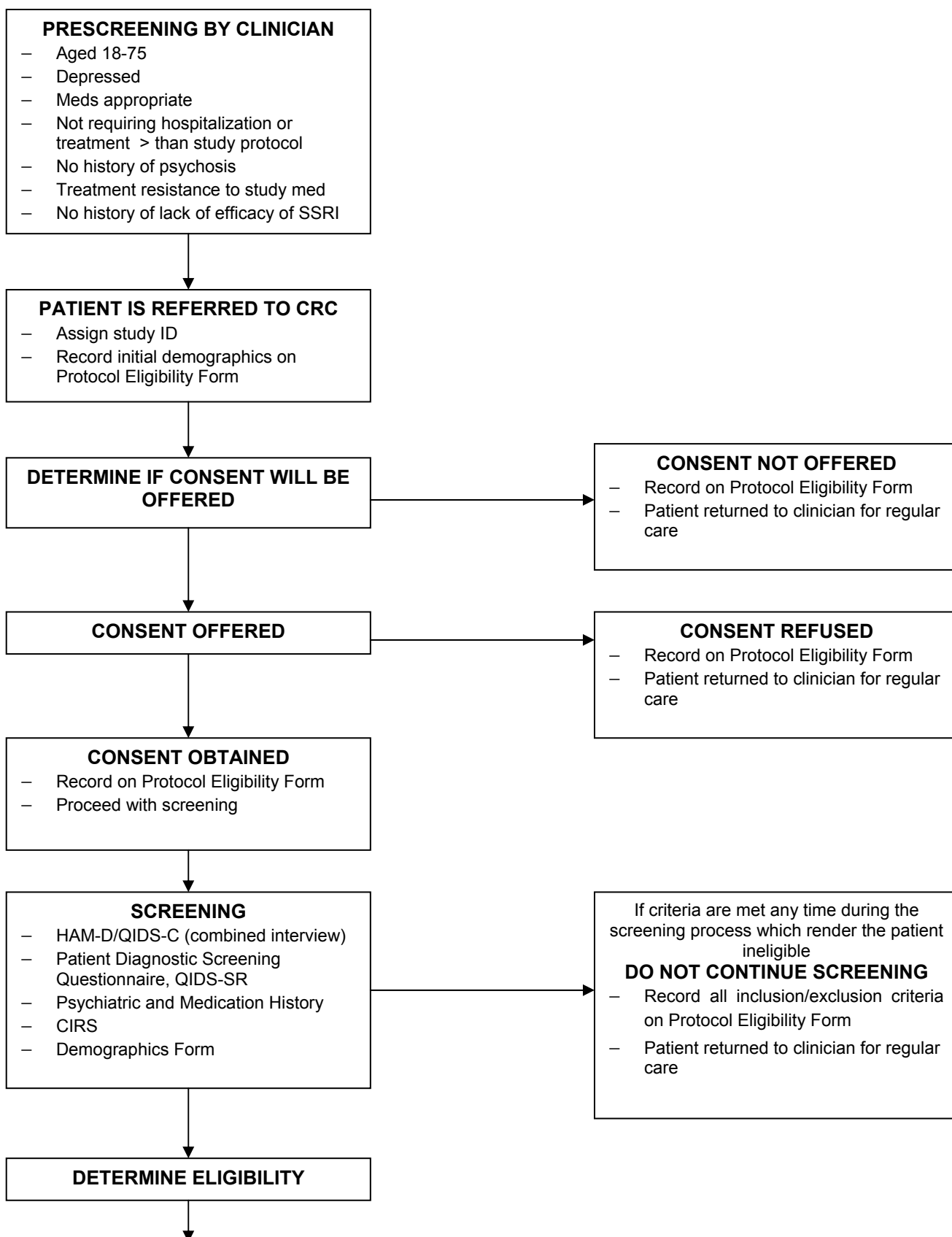
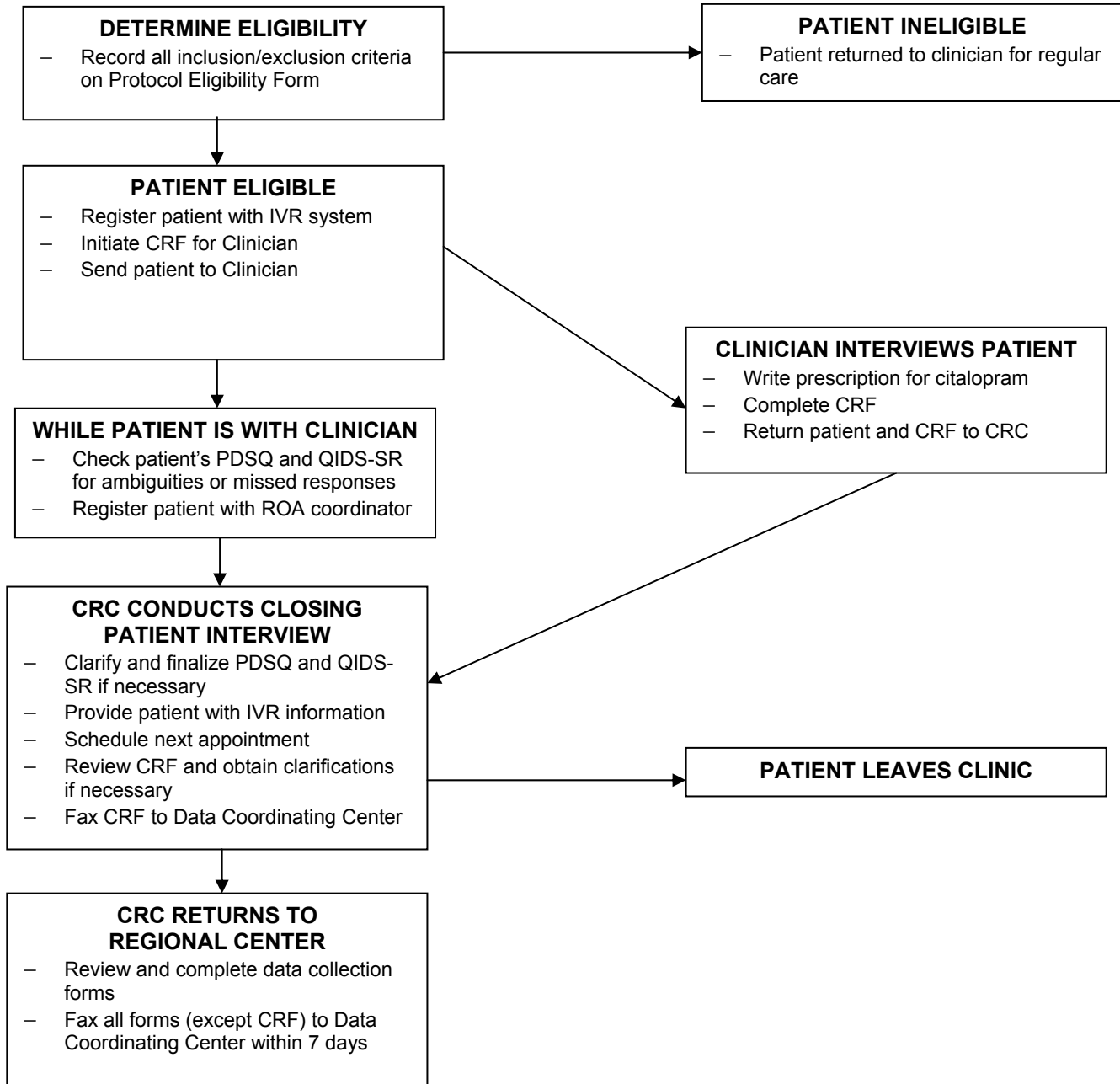




Figure 7. STAR★D Screening Visit Flowchart (Cont.)





## **Obtaining Informed Consent**

### **Study Entry**

Prior to study entry and performing any study-related procedures, the CRC must obtain informed consent.

*Note: Informed consent **must** be obtained from the patient before any study procedures are performed.*

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

- ★ Explains the purpose and requirements of the study using the "Welcome to STAR★D" brochure. It is important that the patient understand the time involved in the increased clinic visits and research outcomes assessments.
- ★ Provides the consent form to the patient for the patient to read. Also provides the study entry consent form summary to the patient.
- ★ Reviews the consent form with the patient, going over the major points.
- ★ Asks the patient at the end if s/he has any questions.
- ★ Answers any questions from the patient.

Who can sign the consent forms:

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

Who cannot sign the consent forms:

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

The patient signs three (3) identical consent forms. One is given to the patient, one is filed in the patient's clinic chart, and the other is filed in the patient's study chart.

***Note: Once the consent to participate in the study is signed, present and ask patient to sign the consent for the economics study.***

*Note: It is suggested that a copy of each patient's consent form(s) should also be placed in a separate binder to remain at the RC at all times.*



### Re-Consenting at Level/Follow-up Change

When a patient moves to a different level or is moved into the follow-up phase, the appropriate consenting procedures for the next level/follow-up must be obtained. The procedures outlined above for obtaining consent must be followed using the appropriate consent form.

*Note: At each subsequent level, a video explaining the availability options and acceptability will be shown prior to signing the consent for that level.*



## STAR ★D Pharmacy Cards

### Card Assignment

The Pharmacy Cards provided by McKesson, Inc. are pre-printed with serial numbers. The 9-digit serial number is comprised of the following:

9 S S S S 9 N N N

where the 4-digit “S” numbers should be the regional center/clinical site code, and the 3-digit “N” numbers will be a sequential number between 001 and 200 for each enrolled patient at a clinical site.

CRCs are to give the Pharmacy Cards to enrolled patients beginning with card number 9xxxx9001 and giving out cards in sequence, not skipping cards.

**The sequence number in the patient’s ID will usually NOT be the same as the sequence number on the pharmacy card.**

Thus the Pharmacy Card given to the first patient enrolled at regional center 34 clinical site 3401 will have the number 934019001, even though that patient’s Study ID might be 3401005XYZ.

The card given to the 34<sup>th</sup> patient enrolled at regional center 32 clinical site 3201 will have the number 932019034, although the patient’s Study ID might contain a sequence number as high 75, making the Study ID 3201075ABC.

When assigning pharmacy cards to patients, **it is very important** that the CRC confirm that the serial number represents both the site number and the next available pharmacy card sequence number.

The serial number should be recorded in the **Screening Log**, and will be required by the IVR system when enrolling the patient.

If a patient loses his/her pharmacy card, the CRC will create a replacement card by writing (in indelible ink) the patient’s original serial number on a blank card, provided by McKesson for replacement purposes.

### Patient Instructions for Use

The CRC explains to the patient how to use the card, including the following information:

- ★ The STAR ★D Pharmacy Card may be used at any pharmacy.
- ★ The patient will present the STAR ★D Pharmacy Card, **not their insurance card**, along with a signed prescription to the pharmacy.
- It is important that the pharmacy submit the claim according to the instructions on the ID card in order to allow the patient to receive the drug free of charge



- ★ There is no co-pay for the medications.
- ★ The card can only be used for STAR★D study medications.
  - If the patient presents the card for other medications, it will be rejected.
- ★ If the patient or pharmacy has any questions regarding the pharmacy card, they should contact McKesson's help line number printed on the pharmacy card (1-800-750-9835). A representative is available at this number from 9:00AM to 6:00PM EST, Monday through Friday (excluding holidays). If the problem cannot be resolved by using this number, the CRC should contact the pharmacist for further information.



## **Instructions for Enrollment and Randomization**

Healthcare Technology Systems (HTS) is providing the Interactive Voice Response (IVR) telephone system to enroll patients into the study, to randomize patients at each new level, to enter patients into follow-up, and to deactivate patients from the study.

The Clinical Research Coordinator will complete a call into this system to:

- 1) Enroll a new patient in the study.
- 2) Make changes in level assignment, including entry into follow-up.
- 3) Deactivate a patient.

Each Clinical Research Coordinator (CRC) will be assigned a unique ID number, which will be used to access the IVR system. This is the first 7 digits of your STAR★D Study ID (see ID Assignment Protocol, page 84). Write your ID number here: \_\_\_\_\_.

In the first call, you will also need to choose a 4-digit password. It's best to pick a number that's easily remembered, such as a combination of numbers from a birth date or the last 4 digits of a friend's phone number. Many people use the year they were born. You will always use your ID number and password to access the system.

**IT IS VERY IMPORTANT THAT YOU STAY ON THE TELEPHONE UNTIL YOU HEAR THE WORDS “THANK YOU AND GOODBYE.”** If you hang up before hearing these words, the patient's status will not be changed and the call will need to be repeated. Please note that during randomization, there may be significant pauses (up to 35 seconds) while the computer assigns the patient to the appropriate treatment. **Please do not hang up during these pauses;** stay on the line until you hear “Thank you and goodbye.”

To access the system, **call 1-800-667-3315**. Enter your ID number. Enter your password.

You will then be asked to enter the ID of the patient that you wish to administer — in this case administer means to enroll, change levels, enter into follow-up or deactivate from the study. You will be asked to confirm that the patient's ID number is correct. The patient ID number is always 7 digits long. The first two digits are the Regional Center code; the third and fourth numbers are the clinical site code, and the last three numbers are the patient sequence number.

Once you've completed the call, a confirmation fax will be generated **to the Regional Center, the NCC, and the DCC**.

### **ENROLLING A NEW PATIENT:**

If the patient is not yet enrolled in the study at this time, you will also be asked to enter the 9-digit pharmacy card number. The system will enroll the patient into **Level 1**.



## CHANGING A PATIENT LEVEL:

The system will first tell you the patient's current level. You'll hear "Patient Number \_\_\_\_\_ is currently at Level \_\_\_\_." Next you'll hear the following choices:

"To randomize this patient to a new level, press 1;

To enter this patient into follow-up, press 2;

To deactivate this patient from the study, press 3."

**If you press 1**, you'll hear the following choices:

"To randomize this patient to level 2, press 1;

To randomize this patient to level 2A, press 2;

To randomize this patient to level 3, press 3;

To randomize this patient to level 4, press 4."

You will then be asked a series of questions regarding the acceptability of each stratum. This is to determine the appropriate stratum in which to randomize each patient. For example, to randomize at level 2, you'll be asked the following questions:

"Is the patient willing to accept a medication switch?

Is the patient willing to accept a medication augmentation?

Is the patient willing to accept a switch to cognitive therapy?

Is the patient willing to accept an augmentation with cognitive therapy?"

After all of the questions have been answered, the system will then proceed to randomize the patient within the appropriate stratum. Once the randomization assignment has been made, the system will announce the appropriate level and the arm to which the patient has been assigned. The system will repeat the information if requested. If none of the treatment options are acceptable, **the system will ask if you intend to exit the patient. If you chose no options in error, you will be given instructions on how to proceed to obtain the randomization. Remember, a call can be aborted by hanging up before hearing the words "thank you and good bye".**



### **ENTERING A PATIENT INTO FOLLOW-UP:**

To enter a patient into follow-up, press 2 when asked.

The system will then enter the patient into follow-up, and will confirm that the patient has been entered into follow-up.

### **DEACTIVATING A PATIENT FROM THE STUDY:**

To deactivate a patient from the study, press 3 when asked.

The system will then deactivate the patient, and will confirm that the patient has been deactivated. If the patient is deactivated from the study in error, you may call back to reactivate the patient.

### **PATIENT INSTRUCTION CARDS:**

Each patient should be given an instruction card. You'll need to write the patient's IVR ID number on the card. Please review the instructions with the patient and give a date by which the IVR call should be completed. Use the calendar printed on the back of the card.

### **TECHNICAL HELP:**

**Call 1-800-316-2414, extension 2460.** If you have technical difficulties, questions about the IVR System, or need further assistance, please call Diane Burroughs, Project Manager at HTS, between the hours of 9 a.m. and 5 p.m. Central Time, Monday through Friday. During office hours, if this number is not answered, please press zero during the voice mail message and another HTS staff member will assist you. Please leave a message after hours.



## Sample Patient Instruction Card

**STAR★D Study/Healthcare Technology Systems, Inc.**  
**Directions for completing the IVR calls**  
**Take this card home with you and keep it handy**

**Each time you call:** Call this toll-free number **1- 800-667-3315**.

Your assigned ID number is: \_\_\_\_\_.

When prompted, enter your ID number. The first time you call, you'll be asked to create a 4-digit password. You'll use the same ID and password each time you call.

Write your password here: \_\_\_\_\_

Answer questions by pressing the keys on the phone. If you want to hear the question again, just wait without answering. The question will be repeated automatically. If you need to pause, press the STAR (\*) key. The system will stay on hold for about 6 minutes. To continue with the call, press the STAR key again. **If the system asks for your telephone number, enter the three digit area code and the telephone number. Do not enter the number 1 first.**

**How to complete the call:** The call is completed when you hear the message "Thank You and Goodbye." **Do not hang up until after you hear "Thank You and Good-bye" at the end of the call.** What if I hang up early? If you accidentally hang up before you hear "Thank You and Good-bye" at the end of the call, the computer won't be able to save your answers. If this happens, call again as soon as you can and repeat the call from the beginning.

**When should I call?** The Clinical Research Coordinator will tell you when to complete your call. You may want to use the calendar on the back of this card to write down the date of your next call.

**What if I have questions?** If you have any questions or concerns related to your emotional or physical health, please contact your doctor right away. If you forget your password or have any questions about the phone system, please call HTS toll free at 1-800-316-2414, extension 2460.

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## Clinic Visit Procedures

Patient visits occur on weeks 0 (baseline), 2, 4, 6, 9, and 12. If at any time during those visits the patient moves to the next level, the schedule is started over with the last visit counting as week 0. For example, if at week 4 the patient is having intolerable side effects and is advanced to Level 2, that visit (week 4) is considered the week 0 for Level 2. The patient will restart the schedule and come back in 2 weeks for week 2 of Level 2.

After the Baseline visit, the procedures for the clinic visits are the same for all weeks and all levels. However, the CRC must be aware of the week in treatment, as this, along with the patient's response is what guides the algorithm. If a patient has missed a visit, there is a window of 6 days around each clinic visit. The critical decision point (CDP) in treatment is at the closest scheduled week number. For example, if a patient has missed week 6 and comes in at week 7, the visit will count as week 6. If a patient has missed week 6 and comes in at week 8, the visit will count as week 9.

Below is an outline of the clinic visit procedures.

★ Patient is given the self-rated measures to fill out prior to being seen by the CRC.

- QIDS-SR<sub>16</sub>
- FISER/GRSEB
- PRISE

*Note: It is very important for the CRC to look over each self-rated measure before the patient leaves to make sure that all items are completed.*

- ★ The CRC administers the appropriate Patient Education material.
- ★ The CRC administers the QIDS-C<sub>16</sub> and discusses any symptoms and side effects that the patient may be experiencing. The CRC should use this time to discuss the research outcomes phone calls to ensure that the calls are being completed on schedule and resolve any problematic issues regarding these calls.
- ★ The CRC completes the appropriate sections of the CRF with the information obtained from the patient.
- ★ Using the Clinical Procedures Manual Guidelines for Treatment, the CRC determines the treatment recommendations according to the response and tolerability of the medication by the patient.
- ★ The CRF is given to the clinician prior to the clinician seeing the patient and the CRC discusses treatment recommendations with the clinician.
- ★ The clinician performs the patient visit, completing remaining sections of the CRF.
- ★ The CRC schedules the next patient visit appointment.



- ★ The CRC faxes a copy of the CRF to the DCC on the same day of the clinic visit. Once a week the CRC will fax the remaining patient visit packet to the DCC.

#### Clinic Visit Payment Procedure:

Clinic payments are generated when the DCC receives the CRF completed for each clinic visit.

Each CRF generates a modest payment to the clinic. If the patient has no third party payment mechanism (i.e., insurance), the clinic is paid an additional amount. This payment is made only if the third party payment item on the CRF is marked NO (e.g. visit is not paid by third party). If third party status is unknown at the time of submission of the CRF, or if it is known that there is a third party coverage, the additional payment is not generated.

#### Payment Adjustment Form:

Sometimes information is discovered after submitting a CRF, which requires notifying the NCC about a change to third party status: For example,

- 1) an insurance company may refuse to cover a visit that was initially thought to be covered (site is due additional payment), or
- 2) it is determined that coverage does apply to a visit which was submitted on the CRF as “unknown”, (no change in payment but the unknown situation is resolved)
- 3) coverage does not apply to a visit which was originally reported as “unknown” (additional payment is due to the site)
- 4) or it is determined that coverage does apply to a visit previously reported as not covered ( site debit may be required). The Payment Adjustment Form is to be completed by the CRC in these cases, so that payments can be adjusted promptly.

(See Q-by-Q for the Payment Adjustment Form for further information on submitting this form.)

#### Phone Visits:

There are circumstances that will require that some of the data collection forms be completed on the telephone. The following procedures are to be used:

If a CRC cannot be at a clinical site when the patient is scheduled to see the clinician, the CRC can collect the required information and relay this information to the clinician before the patient visit. The CRC's assessment is to be done within 24 hours prior to the visit. Once the clinician sees the patient, the clinic visit forms are to be completed and sent to the DCC. The self-report forms are to be completed by the patient at the clinic visit.

If a patient cannot come to the clinic for a scheduled visit, and cannot be rescheduled either within that visit window or for an ad hoc visit, an assessment can be done by phone. The CRC will complete the QIDS and inquire about any problems with side effects of the study treatment, compliance with



treatment, and concomitant medications. The clinician will need to speak with the patient by phone and convey to the patient the treatment plan. The self-report form data are not to be obtained by phone. If the forms can be sent to the patient by fax and can be completed within 24 hours, they can be included in the forms sent to the DCC.

Patients must provide written consent before moving to another level. Therefore, level changes other than level exit cannot be done with a phone visit.

Payment to the clinician for providing a phone visit should be based on the individual clinic's billing policy for phone contacts. The clinic is entitled to the modest fee that each clinic visit provides. The CRF should be marked to reflect the third party status for phone visits at that clinic.

### Level Change/Follow-up

If the patient is to advance to the next level or go into Follow-up, the following procedures are required.

The CRC must:

- ★ Obtain Informed Consent for the appropriate level or Follow-up.
- ★ Complete the Level Exit Form to determine randomization acceptability.
- ★ Call the IVR system to randomize the patient to obtain the treatment assignment for that level.
- ★ Notify the clinician of the randomized treatment that is to be initiated.
- ★ Call the STAR★D Answering Service to notify of a level change.

*Note: This information must be phoned in on the same day, preferably immediately after the visit, in order for the ROAs to contact the patient and obtain the baseline outcome assessment package within the 24-hour window. Please inform the patient of the ROA call and the importance of being available within the 24-hour window.*

The STAR★D Video Scripts (see Appendix H) are provided to assist the CRC in obtaining acceptability at each Level.

### Psychotherapy

If a patient is randomized to cognitive therapy in Level 2, the patient will be referred to the cognitive therapist who is assigned to that clinical site. Since Level 2 treatment begins the day of randomization, the therapist is to be notified the day of randomization of a new patient assignment. The CRC will provide to the therapist the patient's name, study ID, contact information, and any pertinent information concerning the patient's safety.

The CRC will collect data forms from the therapist weekly to fax to the data center.



## Post-Level Follow-up

Once a patient has achieved remission or a response that is deemed satisfactory to the clinician and the patient, the patient will move into the Post Level Follow-up phase. Consent for Follow-up must be obtained according to the procedures outlined in the Obtaining Consent section.

The patient will continue to participate in the Research Outcomes Assessments (both IVR and ROA). The CRC will need to give the patient the following information:

- ★ Schedule of follow-up assessments
  - IVR assessments will be done once a month. A calendar will be provided to the patient as a reminder to call in once a month, preferably on the same day each month.
  - The ROAs will make assessment calls to the patient at months 3, 6, 9, and 12.
- ★ Instructions for breakthrough symptoms
  - If a patient begins to experience the return of depressive symptoms or side effects become intolerable, he/she should call the CRC to schedule an appointment with the clinician if necessary.

*Note: There is not a set schedule for Follow-up clinic visits. STAR ★D data collection forms are not to be completed at clinic visits during Follow-up.*

## **Windows for Scheduling Assessments**

### *Within treatment levels*

The expected date of all assessments within the treatment levels will be based on the date of the week 0 visit for that level.

ROA assessments at level entry are to be completed within **24-72** hours of randomization, **the goal being 24 hours. Any assessment completed after 72 hours will not be included in the primary data set. ROA assessments will be attempted to be collected for 14 days from the time the patient is randomized. ROA assessments will not be completed if more than 14 days have lapsed since randomization.** If the ROA cannot contact the patient within 24 hours, the ROA will contact the CRC to see if the CRC has some insight as to why there has been difficulty contacting the patient. If no contact is made within 2 weeks, the assessment will be considered as missed and a Protocol Deviation form will be completed and faxed to the Data Coordinating Center.

The IVR assessments at level entry can occur before or after the ROA assessment. If a patient has not completed the IVR assessment at level entry within 48 hours of enrollment or randomization, HTS will fax the ROA indicating that the IVR assessment has yet to occur. If no contact is made within 2 weeks, the IVR assessment will be considered as missed. If the patient has not completed the IVR assessment



within 2 weeks, the patient will not be able to access the system to complete the assessment for that time point.

The protocol clinic assessments (2, 4, 6, 9, and 12 weeks) each have a six-day window (+/- six days). If a protocol assessment is not completed within the window, the protocol assessment is considered to be a missed assessment. The CRC is to complete a Protocol Deviation form and fax it to the Data Coordinating Center.

The mid-level IVR assessments have a one-week window (+/- seven days) prior to the due date and 13 days following the due date of the six-week assessment. Calls will be prompted by the CRCs during the four-week assessment. If the patient has not completed the IVR assessment within the window, the patient will not be able to access the system to complete the assessment for that time point. The Data Coordinating Center will monitor mid-level IVR assessments and contact the appropriate CRCs if the assessment has not been conducted as least one day past the due date.

The ROA assessments at level exit are to be completed within 72 hours of exiting level. If the ROA cannot contact the patient within 24 hours, the ROA will contact the CRC to see if the CRC has some insight as to why there has been difficulty contacting the patient. If no contact is made within 2 weeks, the assessment will be considered as missed and a Protocol Deviation form will be completed and faxed to the Data Coordinating Center.

If the patient misses two consecutive ROA assessments, the patient will be dropped from the study. If the ROAs are having difficulties contacting the patient, the CRC may try to schedule the ROA call during a clinic visit.

#### *During follow-up*

The expected date of all assessments within follow-up will be based on the exit date from the treatment levels. Each IVR assessment will take place within a two-week window (+/- two weeks) around the due date of the assessment. The IVR system is designed to prohibit multiple calls for the same time-point. ROA assessments during the follow-up phase will also have a two-week window (+/- two weeks). If the assessment cannot be completed by the halfway point to the next assessment (i.e., six weeks after the due date of the follow-up visit), the ROA is to complete a Protocol Deviation form and fax the form to the Data Coordinating Center.

#### **Time Between Level Exit and Level Entry**

When a patient exits a level and there is no change in clinician from one level to the next, the CRF form for the level exit is considered to be the CRF for entry into the next level. In the instances where the change in level results in a change in clinician, the CRF form from the level exit may be considered if the CRF for entry into the new level if the entry visit for the next level occurs within three days, inclusive, of the level exit visit. If the time is greater than three days, a new level entry packet, including CRF, must be completed for the entry visit. In these instances, a week number of zero (0) is entered onto the data collection forms.



### **Ad Hoc Visits**

Ad hoc visits are those visits that are not part of the standard protocol assessments. These ad hoc visits may occur for a number of reasons, such as the development of side effects. When an ad hoc visit occurs, it is unlikely that the CRC will be at the clinical site therefore, the treating physician will be responsible for completion of a reduced version of the CRF.

When completing the CRF, the treating physician should first indicate that the visit is an ad hoc visit and then complete the reduced version of the CRF. The items that are to be completed on the CRF are indicated by a \*. The CRF and the QIDS-SR<sub>16</sub> are to be given to the CRC the next time the CRC is at the clinical site. The CRC will then check the forms for completeness and fax them to the Data Coordinating Center.

If at all possible, it is preferable that a full set of clinic visit forms be completed at ad hoc visits. The limited data described above is the minimum acceptable data.

### **Study Re-entry**

Patients who drop out of the study in the middle of a level cannot re-enter the study at any time.

Patients who drop out of the study at level exit can re-enter the study within the next four weeks (28 days) if no additional treatments for depression are taken in that time period. At the time of re-entry, the Re-entry (RE) form must be completed and faxed to the Data Coordinating Center. Also, two phone calls are to be made into the IVR system. The first call is to re-activate the patient. The second call will be to randomize the patient to the next level or place in follow-up.

If, at the time of the drop out, the patient was to move on to the next level, the patient should re-enter at the start of that new level. Patients who were to move on to the follow-up phase but dropped out of the study at a level exit and then decide to re-enter the study do so at the point in follow-up where he or she would have been if there had not been a drop out. For example, if after completing a level it was decided that the patient should move on to follow-up and the patient decided to drop out and then three weeks later, the patient returned and was interested in continuing, the patient is to complete the one month follow-up assessments within one week and then continue for the next twelve months in follow-up.

### **Early Termination**

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

1. Patient Choice: Patients may choose not to continue in the study. CRCs will work with the clinician and, if appropriate, the RC Director to understand reasons for this choice and offer reasonable support and treatment alternatives to the patient. However, some patients will choose to discontinue participation.
2. Patient Lost to Follow Up: If a patient has missed visits and the CRC and ROA are unable to contact the patient, the patient is considered "Lost to Follow Up".



3. Noncompliance: If a patient misses more than 10 consecutive days of study medication, including an augmentation drug, the patient should not continue in the study. If the patient misses the equivalent of Cognitive Therapy sessions, the RC Director will consult with the clinician and therapist to determine if the patient can continue in the study( go to the next level). If the patient misses 2 consecutive ROA assessments, they are to be exited from the study.
4. If the patient is inadvertently prescribed a medication that is exclusionary at enrollment (e.g., an anticonvulsant, an antipsychotic, a stimulant), they must be on it for no longer than 24 days and be willing to discontinue it, or they will need to be exited from the study.
5. Administrative Error: Patients who do not meet all study inclusion or exclusion criteria may enter the study in error. Once this is learned, the patient will need to be exited from the study.
6. If a patient in Level 1-4 moves out of the Regional Center area, they will need to be exited from the study. When patients are in Follow-Up and move from the area, they can continue to participate in the study.

The process for terminating patients is as follows:

1. Complete Study Termination Form. Choose the ALL reasons that the patient is leaving the study in Reason for Termination.
2. Complete the Level Exit Form.
3. Call the IVR system and deactivate the patient.
4. Call the ROA Answering Service. If the patient is agreeable to completing the ROA assessment call, give the answering service the standard information. If the patient does not agree to make the call or is lost to follow-up, give the answering service the patient's name and study ID and a message that the ROA is not to contact the patient.
5. The DCC will send a list of patients who have exited the study on a monthly basis to the Clinical Manager and the McKesson representative. This will include the assigned pharmacy card numbers and will be used to deactivate the pharmacy cards.



## ***Suicide Procedures***

### IVR Suicide Notification Procedures

If during an IVR assessment call, a patient has indicated on the QIDS-IVR<sub>16</sub> that he/she is experiencing suicidal thoughts several times a day and has a specific suicide plan, the IVR system will trigger a notification to an answering service. The answering service will notify the CRC for that clinical site (by pager) that the patient is a potential suicide risk. It is important that patients be contacted as soon as possible after such a report to assess current suicide risk and determine if there has been a significant deterioration since the patient was last seen. The Answering Service will provide the CRC with the following information: the patient ID number, date of call and the telephone number that the patient called from to the CRC (if the patient has provided the number). A page will be generated every 15 minutes until a response is obtained. If the CRC does not respond after 2 pages (the first 30 minutes), the Answering Service will then notify the second contact person at the assigned clinical site. If the second contact person does not respond within 15 minutes, the Clinical Manager will be paged. The Clinical Manager and the Safety Officer will coordinate a response.

HTS will also send by fax a notification to the RC Director, the Medical Safety Officers, and the Clinical Manager. This will contain the patient ID number, the date and time of call, the patient's phone number and the suicide item score. HTS will determine which RC to contact by the patient ID number and will follow that RC's instructions on emergency contact.

The HTS system will identify the patient by ID number only; therefore, the CRC must have patient information available at all times.

*Note: It is suggested that the CRC keep a notebook that has a log of ID numbers and patient names and phone numbers. This cannot in any way identify the patient as a STAR ★D patient, i.e., no title on the page to indicate as such. A recommendation is to use a journal/notebook that has a lock on it to preserve/protect patient confidentiality.*

Once the CRC has been notified, he/she should follow the guidelines listed below, as well as the standard procedures for handling suicidal patients used at the specific RC.

### Procedures for Suicidal Patients

In the event that a patient has indicated suicidal ideation with intent or a plan, the following actions must be taken:

- ★ Assess access to means of suicide.
- ★ Assess if patient is alone or has supportive family members or friend with them.
- ★ Contact family members if available.
- ★ Family members should be informed of urgency and limit access to means of suicide.
- ★ CRC is to contact the patient's treating clinician as soon as possible.



If it is determined that the patient is at risk for suicide, complete the SAE Form. If it is determined that the patient is not at risk for suicide, complete the Non-SAE Form.

Each IVR notification must be acknowledged by either an SAE or an NAE form.



## **Cognitive Therapy**

### ***Cognitive Therapist Data Management Training and Certification***

Initial training for the Cognitive Therapists (CT) will take place at the NCC under the direction of Dr. Edward Friedman. This training will include a thorough discussion of the protocol and treatment implementation. At this training session, the CTs will also be trained in the administration of the QIDS-C<sub>16</sub>, and completion of the Clinical Record Form — Cognitive Therapy (CRF-CT) and Therapist Checklist (TC).

Immediately prior to the enrollment of patients into STAR★D, the CT will go through a three-step certification process:

1. Telephone training session
2. Test forms transmission
3. CT certification exam

The first step consists of a telephone training session involving the DCC, the Clinical Manager, and the CT Supervisor. This is a 1-hour training that covers the data management aspects of the study. Topics covered on this call include:

- ★ Forms generation
- ★ Forms completion
- ★ Forms delivery to the CRC
- ★ Filing suggestions
- ★ Web site utilization

The second step will involve the CT completing a test set of data forms, faxing them to the DCC, and sending them to the CRC to ensure proper completion. Finally, the CT will complete a web-based certification exam that covers various procedural aspects of the study. Once all three steps have been completed, the CT is certified for one year.

The CTs will be re-certified annually. The purpose of the re-certification is to ensure that the CTs have current knowledge of the study procedures and protocol, and any procedural changes that may have occurred during the year. The re-certification process will involve a telephone training session involving the DCC, the Clinical Manager, and the CT Supervisor, followed by a web-based re-certification exam.



## ***Procedures For Therapists***

Therapists can get copies of the necessary data collection forms by going to the STAR★D web site ([www.star-d.org](http://www.star-d.org)). On the left hand column, the therapists will click on the ‘Document Sharing’ link. The therapists will be prompted for their website username and password. Next, the therapist will have to click on the ‘Data Collection Forms’ and then “Cognitive Therapy Forms” folders. Here the appropriate ratings packet can be printed for use in the session. In addition, the CT Invoice Form may be printed to track forms completed during treatment sessions.

### Data to be Collected by Study Therapists

If a patient is randomly assigned to receive Cognitive Therapy in Level 2, the therapists will be responsible for collecting the data and sending the forms to the CRCs. The amount and frequency of the data to be collected will depend on whether the patient is receiving Cognitive Therapy alone (CT SWITCH), or as an augment to the treatment with citalopram (CT AUGMENT).

#### CT Switch

For visits during weeks 2, 4, 6, 9 and 12 (only the first visit in weeks 2 and 4), the therapist is to complete the “Full Ratings” packet (includes CRF-CT, TC, QIDS-C<sub>16</sub>, QIDS-SR<sub>16</sub>). For all other visits, the therapist is to complete the “Partial Ratings” packet (TC only).

#### CT Augment

For each visit, the therapist is to complete the “Partial Ratings” packet (TC only).

#### Serious Adverse Events

Any time a serious adverse event (SAE) is noted an SAE form is to be completed and faxed immediately to the Data Coordinating Center at **866-748-PITT (866-748-7488)**. The SAE form can be printed from the STAR★D web site. In addition, the CRC is to be notified immediately. SAEs may be identified by referring to the SAE checklist (page 48).

#### Transmission of Data

At each visit the therapist should mark on the CT Invoice Form those forms that were completed. At the end of each week the therapists will make a copy of all data collection forms completed during the course of the week and mail the originals to the CRCs at the Regional Center, along with the CT Invoice Form. Upon receipt of the data collection forms, the CRC will review the forms and resolve any discrepancies before faxing the forms to the Data Coordinating Center.



### **Monitoring of Protocol Adherence**

Protocol adherence will be monitored by the NCC using the following methods:

- ★ Weekly treatment reports that reflect compliance to the protocol (e.g., visit frequency, dosages, etc.) by RC will be generated by the DCC and sent to the Clinical Manager. The Clinical Manager will review these reports and produce a report by Regional Center detailing the problem areas and possible ways to address the issues.
- ★ Consistent communication between the NCC and RC.
- ★ Monthly enrollment reports by Regional Center.
- ★ Weekly teleconferences with the clinical site clinicians to discuss individual cases, problematic issues, and questions.
- ★ Onsite monitoring visits by the Clinical Manager will be performed on a periodic and as-needed basis.
- ★ Queries will be generated by the DCC to be addressed by the CRC based on the completed CRFs.



# Clinical Procedures Manual

Overview of STAR★D	Levels of Treatment	STAR★D At A Glance Table	Inclusion/Exclusion Criteria	General Principles	Treatment Implementation
	Medication Dosing Table	Side Effects/ Adverse Events	Clinical Research Coordinator	Data Management & Collection	Appendix

## Data Management and Collection

### *ID Assignment Protocol*

Study identifiers (IDs) are provided for all participants in the STAR★D Study, including:

- ★ Regional Centers
- ★ Clinical Sites
- ★ Clinical Research Coordinators (CRCs)
- ★ Research Outcomes Assessors (ROAs)
- ★ Physicians and Cognitive Therapists (Clinicians)
- ★ Patients

Each **Regional Center** will be assigned a two-digit identifier.

The Data Coordinating Center (DCC) will assign IDs for new Regional Centers as they are approved and included in the study. If a Regional Center is excluded from the study, that Center's ID will not be reused for any new Regional Centers. A new ID should be assigned for each new Regional Center.

The first five Regional Centers have been assigned IDs as follows:

- 31 = Southwestern Medical Center, University of Texas
- 32 = Massachusetts General Hospital
- 33 = University of Pittsburgh
- 34 = Columbia University
- 35 = Laureate Healthcare System

Each **Clinical Site** within the Regional Center will be assigned a four-digit identifier, beginning with the two-digit Regional Center identifier and followed with 01 for the first, 02 for the second, etc.

For example, the following Clinical Site IDs have already been assigned:

- 3101 = Family Medicine Clinic, Dallas TX (UTSWMC)
- 3102 = Holiner Psychiatric Group, Dallas TX (UTSWMC)
- 3201 = Charlestown Healthcare Center, Boston MA (Massachusetts General)
- 3402 = LIJ Behavioral Healthcare Group, Long Island NY (Columbia Univ.)

The DCC will assign IDs for each Clinical Site, as each is approved and included in the study. If a Clinical Site is excluded from the study, that Clinical Site's ID will not be reused for any new Clinical Sites. A new ID should be assigned for each new Clinical Site.



Each **Clinical Research Coordinator** (CRC) will be assigned a ten-digit identifier, beginning with the two-digit Regional Center code, followed by two zeros and a sequence number beginning with 701 within each Regional Center. The final three digits will be the first three letters of the CRC's last name.

For example, the following CRC IDs have been assigned at the University of Texas:

3100701STE Diane Stegman  
3100702SHE Eric Shellhorn  
3100703ONE Brandi O'Neal

The **DCC**, by way of a Help Desk request, will be responsible for generating new CRC IDs at the time the CRC is added to the Directory on the STAR★D Web Site.

A current list of CRC IDs may be obtained by selecting the appropriate option in the STAR★D Web Site Directory.

If a CRC leaves the study, the Clinical Manager will deactivate the CRC ID through the Help Desk on the STAR★D Web Site, and will notify both HTS and the DCC. The numbers from that CRC's ID will not be reused for any new CRCs. A new ID should be generated for each new CRC.

Each **Research Outcomes Assessor** (ROA) will be assigned a ten-digit identifier, beginning with 3100, followed by a sequence number beginning with 801, and then the first three letters of the ROA's last name.

ROA IDs have been assigned as follows:

3100801BIG Melanie Biggs  
3100802LAY Michael Lay  
3100803OCH Irene Ochoa  
3100804SOR Elizabeth Soriano  
3100805MOL Miriam Mollett

The **ROA Supervisor** at the NCC will be responsible for generating new ROA IDs at the time the ROA is added to the Directory on the STAR★D Web Site, and will notify the DCC immediately so that ID validation systems may be updated.

A current list of ROA IDs may be obtained by selecting the appropriate option in the STAR★D Web Site Directory.

If an ROA leaves the study, the ROA Supervisor will deactivate the ROA ID through the Help Desk on the STAR★D Web Site, and will notify the DCC. The numbers from that ROA's ID will not be reused for any new ROAs. A new ID should be generated for each new ROA.

Each **Clinician** (physician or cognitive therapist) will be assigned a ten-digit identifier, beginning with the two-digit Regional Center ID, followed by a two-digit clinical site number and a sequence number beginning with 901 within each Regional Center, then the first three letters of the clinician's last name.



For example the following Clinician IDs have been assigned:

**3100 Southwestern Medical Center, University of Texas at Dallas**

3100901HUS Mustafa Husain

**3101 Family Medicine Clinic, Dallas, TX**

3101901CHA Patricia Chandler

3101902WAL Cristen Wall

**3102 Holiner Psychiatric Group, Dallas, TX**

3102901HOL Joel Holiner

3102902MOL Rudy Molina

3102903COR Cliff Cornett

**3200 Massachusetts General Hospital**

3200901FAV Maurizio Fava

**3201 Charlestown Healthcare Center, Boston, MA**

3201901EIS Mark Eisenberg

3201902PEN Barbara Penn

3201903SCH Will Schmitt

The **DCC** at the NCC will be responsible for generating new Clinician IDs at the time the clinician is added to the Directory on the STAR★D Web Site.

A current list of Clinician IDs may be obtained by selecting the appropriate option in the STAR★D Web Site Directory.

If a Clinician leaves the study, the Clinical Manager will deactivate the Clinician ID through the Help Desk on the STAR★D Web Site, and will notify the DCC. The numbers from that Clinician's ID will not be reused for any new Clinicians. A new ID should be generated for each new Clinician.

Each **screened patient** will be assigned a ten-digit identifier, beginning with the four-digit Clinical Site ID, followed by a sequence number beginning with 001 within the Clinical Site, and then the first three letters of the patient's last name.

The **CRC** will assign patient IDs by using the Screening Log for the appropriate Clinical Site (see sample next page). Patients are assigned IDs even if they are not offered consent, or refuse consent, or do not meet inclusion/exclusion criteria. All patients with whom the CRC speaks about the study will be considered to have been screened.

*Note: All **face-to-face screenings** will require the assignment of a Study ID. Patients who never receive a full screening and are excluded based upon a phone call do not require a Study ID.*

Enrolled patients' IDs will be added to ID validation systems at HTS when the CRC calls to enroll a patient. ID validation tables at the DCC will be updated when the Protocol Eligibility Form is received.



Patient IDs will be assigned as in these examples:

3101001\_\_ = [1st patient at Family Medicine Clinic]  
3101002\_\_ = [2nd patient at Family Medicine Clinic]  
3401009\_\_ = [9th patient at LIJ Behavioral Healthcare Group]

If a patient is transferred to a different Clinical Site due to more intensive treatment requirements, the patient ID will not be changed to reflect the new Clinical Site, but will remain as initially assigned.

Each **pharmacy card** will be assigned a nine-digit identifier, beginning with “9”, followed by the four-digit Clinical Site ID, another “9”, and then a three-digit sequence number beginning with 001 within the Clinical Site.

The **CRC** will give pharmacy cards to *enrolled* patients, and will log the pharmacy card numbers on the Screening Log for the appropriate Clinical Site. In most cases, the sequence number on the pharmacy card will be different from the sequence number in the patient Study ID (see sample next page).

Patients who are not offered consent, who refuse consent, or who do not meet inclusion/exclusion criteria will *not* be given pharmacy cards.

Pharmacy card numbers will be added to ID validation systems at HTS when the CRC calls to enroll a patient. ID validation tables at the DCC will be updated when the Protocol Eligibility Form is received.

Pharmacy Card numbers will be assigned as in these examples:

931019001\_\_ = [1st patient **enrolled** at Family Medicine Clinic]  
931019002\_\_ = [2nd patient **enrolled** at Family Medicine Clinic]  
934019009\_\_ = [9th patient **enrolled** at LIJ Behavioral Healthcare Group]

If a patient loses his/her pharmacy card, the CRC will supply a replacement card with the same pharmacy card number. No patient is to be given more than one pharmacy card number.



STAR★D SEQUENCED TREATMENT ALTERNATIVES TO RELIEVE DEPRESSION

RC 31: UTSW MEDICAL CENTER

SITE 3101: FAMILY MEDICINE CLINIC

- SCREENING LOG -

31	01	001	First three letters of last			Full Name	Date screened (mm/dd/yy)	Enrolled (√=yes)	Pharmacy Card Number
			A	L	E				
31	01	002	M	C	M	<i>Duncan McMaster</i>	7/16/01		
31	01	003	F	E	I	<i>Graeme Feiler</i>	7/17/01		
31	01	004	B	O	N	<i>Robin Bonner</i>	7/18/01	√	931019002
31	01	005	K	R	O	<i>David Krouse</i>	8/3/01		
31	01	006	L	I	X	<i>Xiu-Ming Li</i>	8/3/01	√	931019003
31	01	007							
31	01	008							
31	01	009							
31	01	010							
31	01	011							
31	01	012							
31	01	013							
31	01	014							



**Data Collection Forms**

The following table provides a summary of the data collection instruments and protocol.

EL	Protocol Eligibility	CRC				
DM	Demographics	CRC				
CRS	CIRS	CRC				
MHX	Medication History	CRC				
PHX	Psychiatric History	CRC				
QH	Combined HRS-D <sub>17</sub> + QIDS-C <sub>16</sub>	CRC				
PDS	PDSQ	PATIENT				
QS	QIDS-SR <sub>16</sub>	PATIENT				
SC	Screening CRF	PHYSICIAN				
	Enrollment / Randomization by CRC	IVR			IVR	
RA	Combined HRS-D <sub>17</sub> + IDS-C <sub>30</sub>	ROA			ROA	ROA
	QIDS-SR <sub>16</sub>	IVR		IVR-week 6	IVR	IVR
	FISER / GRSEB			IVR-week 6	IVR	IVR
	WSAS / WPAI	IVR		IVR-week 6	IVR	IVR
	SF <sub>12</sub> / Q-LES-Q / UAC-PQ <sub>15</sub>	IVR			IVR	IVR
	PSI				IVR	IVR
QC	QIDS-C <sub>16</sub>			CRC/THERAPIST*		
QS	QIDS-SR <sub>16</sub>			PATIENT		
FG	FISER/GRSEB			PATIENT		
PRS	PRISE			PATIENT		
CC	Clinic Visit CRF			PHYSICIAN		
CT	Cognitive Therapy CRF			THERAPIST*		
TC	Therapist Checklist			THERAPIST*		
LE	Level Exit				CRC	

\* = level 2 only

**EVENT-DRIVEN FORMS:**

		ANY TIME POINT	
PD	Protocol Deviation	CRC	ROA
SAE	Serious Adverse Event	CRC	ROA
NAE	Non-serious Adverse Event	CRC	
ST	Study Termination	CRC	
RE	Study Re-Entry	CRC	



## Forms Generation

STAR★D data collection forms are posted on the study web site as PDF files. They can be printed through Adobe Acrobat Reader, which is a free Internet download (go to URL [www.adobe.com](http://www.adobe.com)). Once printed, these forms may be photocopied.

Sequenced Treatment Alternatives to Relieve Depression

Sponsored by NIMH

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DOCUMENT SHARING (Forms)...

Name	Last Modified	Size	Description
Clinic Visit CRF-CT.pdf	02-Mar-2001 09:34	24K	application/pdf
Clinic Visit CRF.pdf	02-Mar-2001 09:32	31K	application/pdf
Clinic Visit Packet.pdf	13-Dec-2000 14:34	67K	application/pdf
Clinic Visit Self Report.pdf	21-Feb-2001 12:20	28K	application/pdf
Fax Cover Sheet.pdf	22-Feb-2001 13:40	9K	application/pdf
HRS+QIDS Question Sheet.pdf	20-Apr-2001 13:44	19K	application/pdf
Non Serious Adverse Event.pdf	21-Mar-2001 13:46	8K	application/pdf
Off Protocol.pdf	13-Dec-2000 13:56	37K	application/pdf
QIDS Question Sheet.pdf	20-Apr-2001 13:46	12K	application/pdf
ROA Answer Sheet.pdf	08-Feb-2001 15:19	55K	application/pdf

To obtain the forms, click on the document-sharing link on the tool bar (left-hand margin of the front page of the STAR★D web site). Next click on the forms folder. Select the appropriate form(s). Using the EZ-Fill feature, click on the ID and data fields to enter the information online before printing the form (see EZ-Fill description, page \_\_).

When printed forms are photocopied, make sure that all four cornerstones and the form ID (the long number at the top left of the page) remain intact on the copies.

If any of the cornerstones are cut off in the photocopying process, the automated form reader will interpret it as a non-form.

Also, it is very important to obtain clear and unskewed copies so that the forms fax and scan successfully. Smudges or errant dots and lines from dirty photocopyers may inadvertently be read by the scanner as a checked box, and skewed (twisted or crooked) copies will be rejected if the scanner cannot locate responses in their expected positions.

2215405202

STAR★D CLINIC VISIT

CRF Clinician Assessment

Patient ID: \_\_\_\_\_ Date: MM/DD/YYYY

Level: \_\_\_\_\_ Week in level: \_\_\_\_\_

1. Type of visit:  Protocol visit  Ad hoc visit

2. QIDS-C score at the beginning of this treatment level: \_\_\_\_\_

3. Current clinic rating scales: QIDS-C: \_\_\_\_\_ QIDS-SR: \_\_\_\_\_

4. Percent improvement in QIDS-C: \_\_\_\_\_% ((beginning of level - current) / beginning of level) x 100  
If negative change, enter 0

5. Side effect ratings: FISER (frequency): \_\_\_\_\_ FISER (intensity): \_\_\_\_\_ GRSEB: \_\_\_\_\_

6. Is patient menopausal, post-hysterectomy or a male?  NO  YES (if yes, skip to question 8)

7. If no to question 6, enter date of last menstrual period: MM/DD/YYYY

8. Is the patient currently on any STUDY medications?  YES (specify)  NO

CODE	MEDICATION NAME (please print)	TOTAL CURRENT DAILY DOSE	WEEKS AT THIS DOSE
_____	_____	_____mg	_____
_____	_____	_____mg	_____
_____	_____	_____mg	_____
_____	_____	_____mg	_____

\* See medication code list \*\* Record therapy in mcg.

9. Is patient taking Lithium or Nortriptyline?  YES (specify)  NO

MEDICATION TYPE (check one)	MOST RECENT SERUM LEVEL	DATE DRAWN
<input type="checkbox"/> Li <input type="checkbox"/> NTP	_____ (Li MEq/L; NTP ng/ml)	mm/dd/yyyy

CC v2.0 03/01/01

Clinic Visit CRF pg. 1 of 4



There are several different groups of forms, based upon when the forms will be completed (e.g., screening or clinic visit) and who will complete them (CRC, ROA, patient, or clinician).

The CRFs, both screening and clinic visit, are made of 2-part NCR (no carbon required) paper. These forms will be shipped from the NCC. The CRC should notify the STAR ★ D Communication Desk when the CRFs are needed. Please allow 2 weeks for receipt of the forms.

After photocopying, staple the blank forms into the appropriate groups as listed below. Grouped forms may then be clipped together in packets as necessary (e.g., Screening or Clinic Visit) so that all forms for a particular event may be obtained at once.

**Group 1: CRC at Screening**

- Protocol Eligibility
- CIRS
- Medication History
- Psychiatric History
- Combined HRS-D<sub>17</sub> + QIDS-C<sub>16</sub> Interview Text
- Combined HRS-D<sub>17</sub> + QIDS-C<sub>16</sub> Scoring Sheet

**Group 2: Patient at Screening**

- PDSQ
- Demographics
- QIDS-SR<sub>16</sub>

**Group 3: Clinician at Screening**

- Screening CRF

**Group 4: CRC at Clinic Visit**

- QIDS-C<sub>16</sub>

**Group 5: Patient at Clinic Visit**

- QIDS-SR<sub>16</sub>
- FISER/GRSEB
- PRISE

**Group 6: Clinician at Clinic Visit**

- Clinic Visit CRF

**Group 7: Cognitive Therapist Full Packet**

- CRF-CT
- QIDS-C<sub>16</sub>
- QIDS-SR<sub>16</sub>
- TC

**Group 8: Cognitive Therapist Partial Packet**

- TC

**Screening Packet**

**Clinic Visit Packet**

**CT-Switch at Level 2 (only assessments on weeks 0, 2, 4, 6, 9 and 12 (1<sup>st</sup> visit in weeks 2 and 4))**

**CT Augment and CT Switch Level 2**



### **Group 9: ROA**

Combined HRS-D17 + IDS-C30 Interview Text  
Combined HRS-D17 + IDS-C30 Scoring Sheet  
ROA Follow Up Form

### **Group 10: To be used as needed**

Serious Adverse Events  
Non-Serious Adverse Events  
Protocol Deviation  
Level Exit  
Study Termination  
Re-Entry  
SAE Checklist  
Therapist Invoice

## **Forms Completion**

### **I. Keys**

The Patient ID, Clinician ID, ROA ID, CRC ID, date, level, and week in level are all important keys for data collection. All of these fields must be filled out *each time they appear on the form (see EZ Fill description, page \_\_)*. Each page must contain the date of interview, the patient study ID, and if applicable, the CRC/ROA study ID and the clinician study ID. In addition, clinic visit forms will require randomization level (e.g., 1, 2, 2a, 3, or 4), and treatment week within that level (e.g., 2,4,6,9, or 12). Forms missing these data will be returned for correction.

### **II. Acceptable Markings**

Because text fields will be interpreted by a computer, care must be employed when entering text onto a form. Use blue or black ink to complete the forms. Neatly print block capital letters and numbers where required within the boxes provided. Do not allow letters or numbers to connect with the box or the scanner will not distinguish between them. The following will serve as an example:

A	B	C	D	E	F	G	H	I	J	K	L	M
N	O	P	Q	R	S	T	U	V	W	X	Y	Z

1	2	3	4	5	6	7	8	9	0
---	---	---	---	---	---	---	---	---	---

For items that provide check boxes for the answer, either darken the box or neatly place an “X” through the center of the box. Be careful not to over-extend the “X” beyond the box boundaries.



## ACCEPTABLE MARKING OF CHECK BOXES



*Note: The patient's name is not to be written anywhere on the data collection forms that are to be faxed to the DCC. If for some reason, the name needs to be on the form, the CRC should write it on the second sheet of the CRF (yellow sheet).*

### III. Completeness

No blanks should be left on forms, unless the question is not applicable or there is a specified skip pattern.

**Before faxing a form, please review it carefully to ensure all necessary responses are clearly marked.**

### IV. Error Correction

**If an error is made in completing a form DO NOT erase or use white-out.**

It is very important for us to be able to establish the integrity of our data. Any erasures or white-outs on the data collection forms may raise questions for an auditor, so any changes to data (even an accidental mis-mark) must be acknowledged.

For a choice field: If an incorrect response was made, draw a large "X" through it. Enter the correct answer, circle it, and initial and date.

**HFE 3/15/01**



I experience the symptoms often  
I experience the symptoms rarely  
I never experienced the symptoms

For a Key: If an incorrect ID was entered, please obtain a new copy of the form and begin again.

If the form has already been faxed to the Data Coordinating Center, be sure to check the "Update" box in the top right corner of each page before re-faxing.

**Send all pages of a form, even if only one page contains a correction.**



## **Edit Procedures**

On a bi-weekly basis, the Data Coordinating Center will execute editing programs on all data in the STAR ★D database.

These programs will search the data for problems such as:

- ★ **Missing** data
- ★ **Out-of-range** data points
- ★ **Dependency mismatches** (e.g., The question “Does patient consent to be in study?” is marked “Yes”, but data collector has checked some reasons for refusing consent)
- ★ **Logical inconsistencies** (e.g., patient is male, yet date of last menstrual period is recorded)
- ★ **Chronological errors** (e.g., a week 4 visit is dated prior to a week 2 visit)
- ★ **Calculation errors** (e.g., QIDS, HRS-D scores)

These programs will search for both **intraform** (within a single form) and **interform** (across several different forms) inconsistencies.

Reports detailing any inconsistencies will be e-mailed to the data collector every other week for resolution. Reports will list the patient ID, the form(s) in question, the variable(s) in question, the current value, and a message indicating the problem (see sample Edit Report).

Data collectors are to print out the Edit Report, retrieve the original form(s) from the patient file, review the problem(s) as stated on the report, and make changes to the form(s) as necessary.

The methods for making changes to a data collection form are as follows:

- ★ Draw a **large “X”** through the incorrect answer.
- ★ **Mark and circle** the correct answer on the form.
- ★ **Initial and date** the correction.

When a form has had all Edit Report items resolved:

- ★ Check the **“Update” box** on the top right corner of **every page**.
- ★ Fax **every page** of the form to the Data Coordinating Center (even if only one page has a correction).

*NOTE: If an item is determined to be correct as originally coded, the data collector should write “Bypass” on the Edit Report, initial and date it, and fax **that page of** the report back to the Data Coordinating Center, so that subsequent edit programs will not repeatedly report the inconsistency. If an explanation is required, it may be noted on the Edit Report before faxing to the DCC.*



STAR\*D Edit Report  
June 18, 2001

---

**Patient 3101002WEI**

---

**Form: PHX (Psych History) & EL (Eligibility)**

**Date: 05/08/01 Level 1 Week 0**

PHX 7: Symptoms worsening due to menses =Yes  
EL 3: Gender=Male  
Error: Inconsistency between gender and question referring to menses

**Form: QC (QIDS-C<sub>16</sub>)**

**Date: 05/22/01 Level 1 Week 2**

QC 18: Recorded QIDS-C<sub>16</sub> score =13  
Calculated QIDS-C<sub>16</sub> score =11  
Error: Recorded QIDS-C<sub>16</sub> score is not correct.

**Form: CC (Clinic Visit CRF)**

**Date: 05/22/01 Level 1 Week 2**

CC 9: Is patient taking lithium =No  
CC 15: Is lithium dose adjustment needed =No  
Error: If patient not taking lithium, dose adjustment must be 'Not Applicable.'

CC 23: Next appointment date = [missing]  
Error: Cannot be missing

**Form: RA**

**Date: 05/08/01 Level 1 Week 0**

RA 5: Depressed mood = [missing]  
Error: Cannot be missing



## **Faxing Data Collection Forms**

Overview. STAR★D data collection forms will be faxed to the Data Coordinating Center in Pittsburgh at **866-748-PITT (866-748-7488)** for data entry via optical scanning technology. Optical scanning can be very accurate if forms are completed clearly, neatly, and completely.

Faxing forms. The CRF and SAE forms should be reviewed and faxed from the clinical site before leaving the site for the day.

All other forms should be taken back to the Regional Center for review and batch faxing. Batch faxing involves combining all data collection forms collected over days and for multiple patients, and faxing all at once to the Data Coordinating Center. Batch faxing can be done on a daily basis, or may be done with forms accumulated over several days. However, forms must be faxed within 7 days of the clinic visit.

Quality control. Faxed forms should be stored in patient folders with dates recorded for each packet sent. Fax completion reports should be stored in the Data Management Binder provided for that purpose.

The Data Coordinating Center will provide weekly reports of forms received, indicating whether any expected forms are missing. The CRC should verify faxing dates to ensure successful transmission, and should resend any missing forms as indicated on the report.

A Fax Cover Sheet, available from the Document Sharing section of the website, should be used when faxing forms grouped by patient visit. The cover sheet is especially important when forms have been completed in Spanish, or over the phone. This is the only way this information is transmitted to the database.



## ***STAR★D Web Site***

The STAR★ web site ([www.star-d.org](http://www.star-d.org)) will serve as the information dissemination hub for the STAR★ project.

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- Our Mission
- Who We Are
- Treatment Options
- Treatment Protocols
- Implementation

**Ancillary Studies**

- Overview
- General Principles
- Guidelines
- Review Criteria
- Budgetary Aspects
- Reporting
- Regional Center Selection
- Regional Center Questionnaire

**Discussion Groups**

- Therapists Group 1
- CRCs
- Regional Center Directors
- Pharmacotherapy

**STAR★D Organization**

- Directory
- Help Desk
- Document Sharing
- Organization Chart
- Organizational Affiliation
- Protocol

**STAR★D** named as one of the **Web Sites of the Month** by the American Psychological Association : June 2000

<http://www.apa.org/monitor/jun00/website.html>

**WELCOME!**

Currently, practitioners have many effective treatment options for depressed patients, including 20 FDA approved antidepressant medications as well as several time-limited, scientifically tested psychotherapies. However, because no one treatment is universally effective for everyone, many depressed patients do not experience a satisfactory clinical benefit from the initial treatment they receive. Some patients respond to one treatment, some to another, and some may require the combination of two or more treatments. Focusing on the common clinical question of what to do next when patients fail to respond to a standard trial of treatment with an antidepressant medication, STAR★D aims at defining which subsequent treatment strategies, in what order or sequence, and in what combination(s) are both acceptable to patients and provide the best clinical results with the least side effects. Secondly, STAR★D will provide estimates of the costs and cost offsets of such care when provided to outpatients in both primary and specialty care settings.

**MONITOR ON PSYCHOLOGY**  
WASHINGTON, D.C.

Various sections of the web site are only accessible to STAR★D personnel through a password protection system. A number of features on the STAR★D web site are described in the following pages.



## Discussion Groups

Various discussion groups are available on the STAR★D web site. Clicking on “Discussion Groups” on the home page of the web site will display a screen identifying each group. Alternatively, the user could simply click on the name of the desired Discussion Group.

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**About us**

- Our Mission
- Who We Are
- Treatment Options
- Treatment Protocols
- Implementation

**Ancillary Studies**

- Overview
- General Principles
- Guidelines
- Review Criteria
- Budgetary Aspects
- Reporting
- Regional Center Selection
- Regional Center Questionnaire

★ **Discussion Groups**

- Therapists Group 1
- CRCs
- Regional Center Directors
- Pharmacotherapy

**STAR★D Organization**

- Directory
- Help Desk

### DISCUSSION GROUPS...

- **Therapists Forum Group 1**  
The therapists forum will allow therapists to discuss treatment alternatives, care issues and STAR★D study progress.
- **CRCs Forum**  
The Clinical Research Coordinators forum will allow CRCs to discuss issues related to treatment and data collection protocols.
- **Regional Center Directors**  
The Regional Center Directors forum will allow Regional Center Directors and Associate Directors to discuss issues related to day-to-day administrative procedures and infrastructure.
- **Pharmacotherapy**  
The Pharmacotherapy forum will allow treating physicians to discuss drug treatment regimens, care issues and STAR★D study progress.

These Discussion Groups provide a forum to post questions and discuss issues relevant to a select group of STAR★D investigators and clinicians. Each group is only open to relevant individuals, so the user will be required to supply his/her password before being allowed access to the Discussion Group.



## Directory

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**About us**

- Our Mission
- Who We Are
- Treatment Options
- Treatment Protocols
- Implementation

**Ancillary Studies**

- Overview
- General Principles
- Guidelines
- Review Criteria
- Budgetary Aspects
- Reporting
- Regional Center Selection
- Regional Center Questionnaire

**Discussion Groups**

- Therapists Group 1
- CRCs
- Regional Center Directors
- Pharmacotherapy

**STAR\*D Organization**

- Directory
- Help Desk
- Document Sharing
- Organization Chart
- Organizational Affiliation
- Protocol

Sort by: name

name  
affiliation  
committee/group

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

**A**

<b>Perrie Adams, Ph. D.</b> National Coordinating Center - University of Texas	UT Southwestern Medical Center 5323 Harry Hines Blvd Dallas, TX 75235	Telephone: (214) 648-2258 Fax: (214) 648-7980 <a href="mailto:padams@sw103a.swmed.edu">padams@sw103a.swmed.edu</a>
<b>George Alexopolous, M. D.</b>	The New York Hospital - Cornell Medical Center 21 Bloomingdale Rd White Plains, NY 10605	Telephone: (914) 997-5767 Fax: (914) 997-5926 <a href="mailto:gsalexop@med.cornell.edu">gsalexop@med.cornell.edu</a>
<b>Jonathan Alpert, M.D., Ph. D.</b> <b>Associate Director</b> Massachusetts General Hospital	Massachusetts General Hospital 15 Parkman Street WAC 8125 Boston, MA 02114	Telephone: (617) 726-5948 Fax: (617) 724-3028 <a href="mailto:jalpert@partners.org">jalpert@partners.org</a>
<b>Martha Anderson</b> <b>Administrative Coordinator</b> Columbia University	New York State Psychiatric Institute 1051 Riverside Drive New York, NY 10032	Telephone: (212) 543-5786 Fax: (212) 543-5326 <a href="mailto:anderso@pi.cpmc.columbia.edu">anderso@pi.cpmc.columbia.edu</a>

The STAR\*D Project Directory may be displayed by clicking on the “Directory” link on the home page.

The directory contains an entry for all personnel in the project, and may be displayed in one of three sort orders: *name*, *affiliation*, or *committee/group*. Clicking on a letter of the alphabet moves the display to that point in the directory.



The directory is a protected area of the STAR★D web site accessible to all those with a STAR★D username and password. The directory provides necessary contact information for all STAR★D study personnel. The initial information for each person included in the STAR★D directory will be entered into the system by the staff at the Data Coordinating Center. If during the course of the study, the contact information for a given individual changes (e.g., change in telephone number), the individual will be responsible for changing the information in the directory. This can be done by clicking on the name of the individual, make the necessary changes to the information in the text boxes and then clicking on the submit button. Please note that the system is designed so that any given person can only change their information. The access to make changes is based on the user name of the individual.



## Help Desk

The Help Desk is a utility available on the STAR★D Web Site through which STAR★D personnel may review Frequently Asked Questions (FAQs) or may submit requests for service, such as asking questions or requesting help with problems. The user will receive notification of the solution to his/her request via email.

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**About us**

- Our Mission
- Who We Are
- Treatment Options
- Treatment Protocols
- Implementation

**Ancillary Studies**

- Overview
- General Principles
- Guidelines
- Review Criteria
- Budgetary Aspects
- Reporting
- Regional Center Selection
- Regional Center Questionnaire

**Discussion Groups**

- Therapists Group 1
- CRCs
- Regional Center Directors
- Pharmacotherapy

**STAR★D Organization**

- Directory
- Help Desk
- Document Sharing
- Organization Chart
- Organizational Affiliation
- Protocol

**Help Desk Options**

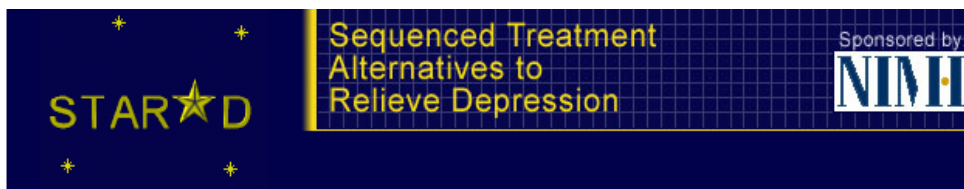
**Step 1**  
Check STAR★D's Frequently Asked Questions

**Step 2**  
Enter a Request for Assistance  
Filling out this form will notify the correct person at STAR★D by email and will log your problem into the STAR★D Help Desk Database.

\*Help Desk Administration Only

To check STAR★D's FAQs:

- Enter one or more words to begin the FAQ search.
- Select 'and' if the search is to show only those FAQs that contain all the specified words.
- Select 'or' if you would like the search to show those FAQs that contain any of the words.



### Help Request Form

**Name:**

**Phone Number:**   
(not required)

**Fax Number:**   
(not required)

**Location:**

**Request Category:**

**Brief Description of Request:**

**Deadline Date:**   
(not required)

**Full Description of Request:**

**In your estimation is this request:**

- Urgent (work cannot continue)**
- High Priority**
- Medium Priority**
- Low Priority**

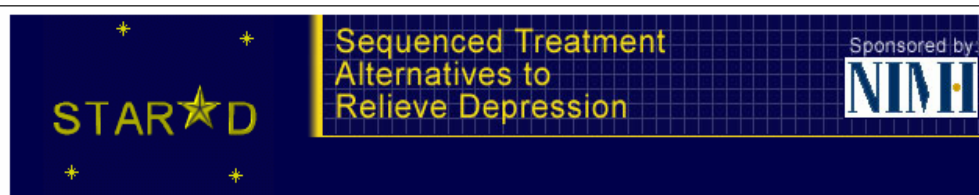
**Confirm Reading**

To Enter a Request for Assistance: Click on “Help Desk” and enter user name and password.

**Name, phone, fax number, and location** will be automatically inserted from the STAR★D directory based on the user’s log-in information.

**Request Category:** This is a drop-down box that lists different categories for questions or problem. It is important that the category that best fits the help desk request be selected. The appropriate STAR★D personnel will receive the help desk request based upon the category chosen.

*[Help Desk continued on next page]*



## Help Request Form

**Name:**

**Phone Number:**   
(not required)

**Fax Number:**   
(not required)

**Location:**

**Request Category:**

**Brief Description of Request:**

**Deadline Date:**   
(not required)

**Full Description of Request:**

**In your estimation is this request:**

Urgent (work cannot continue)  
 High Priority  
 Medium Priority  
 Low Priority

Confirm Reading

**Brief Description of Request:** Enter a one-line statement that summarizes the question or problem.

**Deadline Date:** This field may be left blank unless there is an applicable deadline date.

**Full Description of Request:** Enter a full description of the question or problem, giving as much detail as possible.

**Priority:** Select the urgency or priority of the request.

**Confirm Reading:** The user will automatically receive an e-mail confirming that a request has been sent. Clicking the **Confirm Reading** box will cause another e-mail to be sent when someone has received and read the request.

**Submit/Reset/Cancel:** Click the **Submit** button to send the request; **Reset** will clear the form to be completed anew; **Cancel** will return the user to the Help Desk screen.



## Document Sharing

A number of different document types can be read and printed directly from the STAR★D web site. These include data collection forms, minutes from meetings and conference calls, operations memos, and other data management documentation.

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**About us**

- Our Mission
- Who We Are
- Treatment Options
- Treatment Protocols
- Implementation

**Ancillary Studies**

- Overview
- General Principles
- Guidelines
- Review Criteria
- Budgetary Aspects
- Reporting
- Regional Center Selection
- Regional Center Questionnaire

**Discussion Groups**

- Therapists Group 1
- CRCs
- Regional Center Directors
- Pharmacotherapy

**STAR★D Organization**

- Directory
- Help Desk
- Document Sharing
- Organization Chart
- Organizational Affiliation
- Protocol

DOCUMENT SHARING (Forms)...

Name	Last Modified	Size	Description
Forms	21-May-2001 12:27	-	Folder (sub-directory)
Minutes	22-Feb-2001 16:43	-	Folder (sub-directory)
Operations Memos	21-Jun-2001 16:08	-	Folder (sub-directory)
Q by Q	21-May-2001 12:30	-	Folder (sub-directory)
Variable Reference	21-May-2001 12:28	-	Folder (sub-directory)

**Notice:**  
You need the **Adobe Acrobat Reader** to view and print PDF files.

Get Acrobat Reader

In order to access documents on the web site, the user must have Adobe Acrobat Reader v5.0 (a free download) loaded on his/her computer. Acrobat can be downloaded by clicking on the yellow Adobe icon on the document-sharing page.



Clicking on the desired folder (*Forms, Minutes, Operations Memos, Q by Q, Variable Reference*) will open a screen listing available documents in the folder.

Clicking on a specific document in the list will cause that document to be displayed on the user's screen.

6872351855

**STAR★D SCREENING**

Patient ID \_\_\_\_\_

**PROTOCOL ELIGIBILITY**  update  
**Clinician Assessment**

Date MM / DD / YYYY

1. Last 4 digits of social security number \_\_\_\_\_

2. Date of Birth MM / DD / YYYY

3. Gender (Check one)  
 Male  Female

4. Race/ethnicity (check one or more)  
 White  Black or African American  Asian  
 Hispanic or Latino  American Indian or Alaskan Native  Native Hawaiian or Other Pacific Islander

5. Was patient offered consent?  Yes (skip to question 6 on next page)  
 No (continue with questions below)

Reason(s) not offered consent (check all that apply):

- History of mania, unequivocal hypomania, or bipolar disorder
- History of psychotic symptoms
- Current anorexia or bulimia
- Current primary obsessive compulsive disorder

The document can be printed by clicking on the printer icon at the top of the screen, or by selecting "Print ..." from the File dropdown menu at the top of the screen (see area circled in red).

## Reports

A number of reports are available on the STAR★D web site and additional reports will be added as the study progresses. Access to these reports will be dependent on the type of report and the individual accessing the reports role in the study.



### **Document Storage**

One copy of the consent form and the original copy of the CRF should be kept in the patient's file. The remaining paperwork (i.e., rating scales, intake forms, duplicate copy of CRF, etc.) should be kept in a patient folder/binder to be stored at the Regional Center.

All study files are to be kept by the Regional Center for five years after the last patient at any site has exited the study. The DCC will notify the Regional Centers when this occurs. The NCC will then notify the Regional Center Directors.

### **Filing Suggestions**

- ★ One hanging (pendaflex) file for each enrolled patient.
- ★ One hanging file for each clinic to hold Protocol Eligibility Forms for non-enrolled patients.
- ★ Keep hanging files in patient ID order.
- ★ Keep Screening and Clinic Visit packets stored in hanging file in date order.

Each CRC receives a data management binder from the Data Coordinating Center. Documents to be stored in the binder include the fax completion reports, form status reports, edit reports, and operations memos.



## **Operations Memos**

The study will use operations memos to document administrative decisions and ongoing instructions for the conduct of the study. Operations memos will be sequentially numbered. Memos that address specific issues will be sent via email directly to relevant personnel (e.g., issues related to the completion of the CRF-CT will be sent to the cognitive therapists at the clinical sites) and always to the CRCs at each Regional Center. The CRCs will store these memos in the Data Management binder provided by the Data Coordinating Center. In addition, all operations memos will be emailed to Dr. Madhukar Trivedi (Co-Director of the NCC), the Clinical Manager, the Operations Manager, and the NIMH Program Coordinator. All STAR★D personnel may obtain copies of the operations memos by visiting the document sharing portion of the STAR★D Web Site [www.star-d.org](http://www.star-d.org).

Memos that contain urgent or time-sensitive information and require the immediate attention of the CRC will be faxed directly to the Regional Center. The Administrative Assistant at the Regional Center will immediately deliver the memo or relay the information to the CRC.



# Clinical Procedures Manual

Overview of STAR★D	Levels of Treatment	STAR★D At A Glance Table	Inclusion/Exclusion Criteria	General Principles	Treatment Implementation
	Medication Dosing Table	Side Effects/ Adverse Events	Clinical Research Coordinator	Data Management & Collection	<b>Appendix</b>

## Appendix

### A. DSM-IV Criteria for Major Depressive Disorder

### B. Tables of Study Procedures

- ★ Table 1. Schedule of Screen and Baseline Assessments
- ★ Table 2. Research Outcomes Assessment Battery
- ★ Table 3. Schedule of Evaluations for Follow-up
- ★ Table 4. Schedule of Measures Acquired at Clinic Visits

### C. Medication Information

- ★ Antidepressant Medications
- ★ Augmentation Agents
- ★ Guidelines for Adequate Treatment Trials of Antidepressants
- ★ Rules for Tapering Medications
- ★ Rules for Switching to a MAOI

### D. Forms and Process Measures Used for the Screening Visit (with instructions for completion)

- ★ Screening Checklist
- ★ Eligibility
- ★ Demographics
- ★ Cumulative Illness Rating Scale (CIRS)
- ★ Medication History
- ★ Psychiatric History
- ★ Hamilton Depression Rating Scale – 17 Item (HRS-D<sub>17</sub>)/Quick Inventory of Depressive Symptomatology - Clinician-Rated (QIDS-C<sub>16</sub>) – Combined Interview
- ★ Psychiatric Diagnostic Screening Questionnaire (PDSQ)



- ★ Quick Inventory of Depressive Symptomatology - Self-Report (QIDS-SR<sub>16</sub>)

- ★ Clinical Record Form (CRF) — Screening

**E. Forms and Process Measures for the Clinic Visit** (with instructions for completion)

- ★ Clinic Visit Checklist

- ★ Clinical Record Form (CRF)

- ★ Quick Inventory of Depressive Symptomatology - Clinician-Rated (QIDS-C<sub>16</sub>)

- ★ Quick Inventory of Depressive Symptomatology - Self-Report (QIDS-SR<sub>16</sub>)

- ★ Frequency and Intensity of Side Effects Rating/Global Rating of Side Effect Burden (FISER/GRSEB)

- ★ Patient Rated Inventory of Side Effects (PRISE)

**F. Miscellaneous Forms**

- ★ Clinical Record Form — Cognitive Therapy (CRF-CT)

- ★ Therapist Checklist

- ★ Level Exit Form

- ★ Protocol Deviation Form

- ★ Serious Adverse Events (SAEs)

- ★ SAE Checklist

- ★ NSAE Form

- ★ Study Termination

- ★ Study Reentry

- ★ Medication Code List

**G. IVR Scripts**

- ★ CRC Enrollment/Randomization Call

- ★ Baseline Patient Assessment

- ★ Mid-level/Interim Assessment

- ★ Level Exit/Quarterly/Monthly Assessment



## **H. Video Scripts**

- ★ Script For Participants Who Are Eligible to Enter Level 2
- ★ Script For Participants Who Are Eligible to Enter Level 2A
- ★ Script For Participants Who Are Eligible to Enter Level 3
- ★ Script For Participants Who Are Eligible to Enter Level 4

## **I. Communications**

- ★ Important Phone Numbers





## **DSM-IV Criteria for Major Depressive Disorder**

### **Criteria for Major Depressive Episode**

- A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

**Note:** Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

- (1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). **Note:** In children and adolescents, can be irritable mood.
  - (2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
  - (3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains.
  - (4) insomnia or hypersomnia nearly every day
  - (5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
  - (6) fatigue or loss of energy nearly every day
  - (7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
  - (8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
  - (9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
- B. Symptoms do not meet criteria for a Mixed Episode.
- C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
- E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.



### **Diagnostic criteria for 296.2x Major Depressive Disorder, Single Episode**

- A. Presence of a single Major Depressive Episode.
- B. The Major Depressive Episode is not better accounted for by Schizoaffective Disorder and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.
- C. There has never been a Manic Episode, A Mixed Episode, or a Hypomanic Episode. **Note:** This exclusion does not apply if all of the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment induced or are due to the direct physiological effects of a general medical condition.

*Specify* (for current or most recent episode):

#### **Severity/Psychotic/Remission Specifiers**

**Chronic**

**With Catatonic Features**

**With Melancholic Features**

**With Atypical Features**

**With Postpartum Onset**

### **Diagnostic criteria for 296.3x Major Depressive Disorder, Recurrent**

- A. Presence of two or more Major Depressive Episodes.  
**Note:** To be considered separate episodes, there must be an interval of at least 2 consecutive months in which criteria are not met for a Major Depressive Episode.
- B. The Major Depressive Episodes are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.
- C. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode. **Note:** This exclusion does not apply if all of the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment induced or are due to the direct physiological effects of a general medical condition.

*Specify* (for current or most recent episode)

#### **Severity/Psychotic/Remission Specifiers**

**Chronic**

**With Catatonic Features**

**With Melancholic Features**

**With Atypical Features**

**With Postpartum Onset**



*Specify:*

**Longitudinal Course Specifiers (With and Without Interepisode Recovery)  
With Seasonal Pattern**



**Table 1. Schedule of Screen and Baseline Assessments**

Screening Assessments						
Domain	Measure	Time	How	When	Who	Where
<b>Intake</b>						
Consent	Consent	20 min	Interview	At Intake	CRC	Clinic
Characteristics	Clinical/ Demographic Features	3 min	Interview	At Intake	CRC	Clinic
Eligibility	Inclusion/Exclusion	5 min	Interview	At Intake	CRC	Clinic
Diagnosis	PDSQ	20-30 min	Self-report	At Intake	Patient	Clinic
Symptoms	HRS-D <sub>17</sub> /QIDS-C <sub>16</sub>	15 min	Interview	At Intake	CRC	Clinic
	QIDS-SR <sub>16</sub>	6 min	Self-report	At Intake	Patient	Clinic
GMCs	CIRS	5 min	Interview	At Intake	CRC	Clinic

**Baseline Research Outcome Assessments**

Symptoms	HRS-D <sub>17</sub> /IDS-C <sub>30</sub>	20-25 min	Telephone	Within 24 hrs of Intake	ROA	Home/Work
	QIDS-IVR <sub>16</sub>	6 min	Telephone	Within 24 hrs of Intake	IVR	Home/Work
Function	SF-12	4 min	Telephone	Within 24 hrs of Intake	IVR	Home/Work
	WSAS	2 min	Telephone	Within 24 hrs of Intake	IVR	Home/Work
	WPAI	2.5 min	Telephone	Within 24 hrs of Intake	IVR	Home/Work
Quality of Life	Q-LES-Q	6 min	Telephone	Within 24 hrs of Intake	IVR	Home/Work
Side Effects	N/A	N/A	N/A	N/A	N/A	N/A
Patient Satisfaction	N/A	N/A	N/A	N/A	N/A	N/A
Utilization & Cost	UAC PQ-15	5 min	Telephone	Within 24 hrs of Intake	IVR	Home/Work

\*\*Screening and baseline research outcomes assessments are obtained on protocol patients (n=4,000).

GMCs = General Medical Conditions

IVR = Interactive Voice Response

ROA = Research Outcomes Assessor

CIRS = Cumulative Illness Rating Scale

HRS-D<sub>17</sub> = Hamilton Rating Scale for Depression (17-item)

IDS-C<sub>30</sub> = Inventory of Depressive Symptomatology – Clinician-Rated (30-item)

QIDS-C<sub>16</sub> = Quick Inventory of Depressive Symptomatology – Clinician-Rated (16-item)

QIDS-IVR<sub>16</sub> = Quick Inventory of Depressive Symptomatology – Interactive Voice Response (16-item)

QIDS-SR<sub>16</sub> = Quick Inventory of Depressive Symptomatology – Self-Report (16-item)

Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire (16-item)

PDSQ = Psychiatric Diagnostic Screening Questionnaire

SF-12 = Short-Form Health Survey (12-item)

UAC PQ-15 = Utilization and Cost Patient Questionnaire (15-item)

WPAI = Work Productivity & Activity Impairment Questionnaire (6-item)

WSAS = Work & Social Adjustment Scale (5-item)



**Table 2. Research Outcomes Assessment Battery**

<b>Domain</b>	<b>Measure</b>	<b>Time</b>	<b>How</b>	<b>Who</b>	<b>Where</b>
<b>Symptoms</b>	HRS-D <sub>17</sub> /IDS-C <sub>30</sub>	20-25 min	Telephone	ROA	Home/Work
	QIDS-IVR <sub>16</sub> *	6 min	Telephone	IVR	Home/Work
<b>Function</b>	SF-12	4 min	Telephone	IVR	Home/Work
	WSAS*	2 min	Telephone	IVR	Home/Work
	WPAI*	2.5 min	Telephone	IVR	Home/Work
<b>Quality of Life</b>	Q-LES-Q	6 min	Telephone	IVR	Home/Work
<b>Side Effects</b>	FISER/GRSEB*	1.5 min	Telephone	IVR	Home/Work
<b>Patient Satisfaction</b>	PSI	1 min	Telephone	IVR	Home/Work
<b>Utilization &amp; Cost</b>	UAC PQ-15	5 min	Telephone	IVR	Home/Work
<b>Income</b>	IPAQ	2 min	Telephone	ROA	Home/Work

All outcomes assessments are obtained at the exit from each treatment level and in follow-up at months 3, 6, 9, and 12.

\* Obtained at Week 6 of each level.

ROA = Research Outcomes Assessor

IVR = Interactive Voice Response

FISER/GRSEB = Frequency and Intensity of Side Effects Rating/Global Rating of Side Effects Burden

HRS-D<sub>17</sub> = Hamilton Rating Scale for Depression (17-item)

IDS-C<sub>30</sub> = Inventory of Depressive Symptomatology – Clinician-Rated (30-item)

IPAQ = Income and Public Assistance Questionnaire (5-item)

PSI = Patient Satisfaction Inventory (2-item)

Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire

QIDS-IVR<sub>16</sub> = Quick Inventory of Depressive Symptomatology – Interactive Voice Response (16-item)

SF-12 = Short-Form Health Survey (12-item)

UAC PQ-15 = Utilization and Cost Patient Questionnaire (15-item)

WPAI = Work Productivity & Activity Impairment Questionnaire (6-item)

WSAS = Work & Social Adjustment Scale (5-item)



**Table 3. Schedule of Evaluations for Follow-up**

<b>Domain</b>	<b>Measure</b>	<b>Time</b>	<b>How</b>	<b>When</b>	<b>Who</b>	<b>Where</b>
<b>Post-Level Follow-up</b>						
<b>Symptoms</b>	HRS-D <sub>17</sub> /IDS-C <sub>30</sub>	20-25 min	Telephone Call	Months 3, 6, 9, 12	ROA	Home/Work
	QIDS-IVR <sub>16</sub>	6 min	Telephone	Months 3, 6, 9, 12	IVR	Home/Work
<b>Function</b>	SF-12	4 min	Telephone	Months 3, 6, 9, 12	IVR	Home/Work
	WSAS	2 min	Telephone	Months 3, 6, 9, 12	IVR	Home/Work
	WPAI	2.5 min	Telephone	Months 3, 6, 9, 12	IVR	Home/Work
<b>Quality of Life</b>	Q-LES-Q	6 min	Telephone	Months 3, 6, 9, 12	IVR	Home/Work
<b>Utilization &amp; Cost</b>	UAC PQ-15	5 min	Telephone	Months 3, 6, 9, 12	IVR	Home/Work
<b>Side Effects</b>	FISER/GRSEB	1.5 min	Telephone	Months 3, 6, 9, 12	IVR	Home/Work
<b>Patient Satisfaction</b>	PSI	1 min	Telephone	Months 3, 6, 9, 12	IVR	Home/Work
<b>Post-Level Follow-up Interim Research Evaluations</b>						
<b>Symptoms</b>	QIDS <sub>16</sub>	6 min	Telephone	Months 1,2,4,5, 7,8,10,11	IVR	Home/Work
<b>Function</b>	WSAS	2 min	Telephone	Months 1,2,4,5, 7,8,10,11	IVR	Home/Work
	WPAI	2.5 min	Telephone	Months 1,2,4,5, 7,8,10,11	IVR	Home/Work
<b>Side Effects</b>	FISER/GRSEB	1.5 min	Telephone	Months 1,2,4,5, 7,8,10,11	IVR	Home/Work

IVR = Interactive Voice Response

FISER/GRSEB = Frequency & Intensity of Side Effects Rating/ Global Report of Side Effect Burden

HRS-D<sub>17</sub> = Hamilton Rating Scale for Depression (17-item)

IDS-C<sub>30</sub> = Inventory of Depressive Symptomatology – Clinician-Rated) (30-item)

PSI = Patient Satisfaction Inventory

QIDS-IVR<sub>16</sub> = Quick Inventory of Depressive Symptomatology – Interactive Voice Response (16-item)

Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire

SF-12 = Short-Form Health Survey (12-item)

UAC PQ-15 = Utilization and Cost Patient Questionnaire (15-item)

WPAI = Work Productivity & Activity Impairment Questionnaire (6-item)

WSAS = Work & Social Adjustment Scale (5-item)



**Table 4. Schedule of Measures Acquired at Clinic Visits\***

<b>Domain</b>	<b>Measure</b>	<b>Time</b>	<b>How</b>	<b>Who</b>	<b>Where</b>	<b>When</b>
<b>Symptom</b>	CGI-I	1/2 min	Interview (1-item)	CLIN	Clinic	All Visits
	QIDS-C <sub>16</sub>	6 min	Interview (16-item)	CRC/CLIN	Clinic	All Visits
	QIDS-SR <sub>16</sub>	6 min	Self Report (16-item)	Patient	Clinic	All Visits
<b>Side Effects</b>	FISER/GRSEB	1.5 min	Self Report (3-item)	Patient	Clinic	All Visits
	PRISE	3 min	Self Report (8-item)	Patient	Clinic	All Visits

\*Note: These measures are used to provide consistent information to the clinicians who use this information in the protocol and are recorded on the CRF.  
Clinic visit measures are collected at clinic visits for patients in protocol treatment and for patients seen in follow-up.

CGI-I = Clinical Global Impression — Improvement

FISER = Frequency & Intensity of Side Effect Rating

GRSEB = Global Rating for Side Effect Burden

PRISE = Patient Rated Inventory of Side Effects

QIDS-C<sub>16</sub> = Quick Inventory of Depressive Symptomatology - Clinician-Rated (16-item)

QIDS-SR<sub>16</sub> = Quick Inventory of Depressive Symptomatology - Self-Report (16-item)



## **Communications**

### ***Important Phone Numbers***

**STAR★D National Coordinating Center**  
**University of Texas**  
**Southwestern Medical Center at Dallas**  
Department of Psychiatry  
UT Southwestern Medical Center  
5323 Harry Hines Blvd  
Dallas, TX 75390-9086  
214-648-4600 – Tel  
877-757-3444 – Fax

Principal Investigator  
Director, National Coordinating Center  
**A. John Rush, M. D.**  
214-648-4600 – Tel  
877-757-3444 – Fax  
[john.rush@utsouthwestern.edu](mailto:john.rush@utsouthwestern.edu)

Co-Director, National Coordinating Center  
**Madhukar H. Trivedi, M. D.**  
UTSWMC  
Department of Psychiatry  
UT Southwestern Medical Center  
5323 Harry Hines Blvd  
Dallas, TX 75390-9101  
214-648-4282 - Tel  
214-648-4210 - Fax  
800-946-4646 - Pin #1428347 - Pager  
[madhukar.trivedi@utsouthwestern.edu](mailto:madhukar.trivedi@utsouthwestern.edu)

Clinical Manager  
**Diane Stegman, RN,C**  
214-648-4622 – Tel  
**214-648-4612** – Fax  
**888-322-6747** – Pager  
[diane.stegman@utsouthwestern.edu](mailto:diane.stegman@utsouthwestern.edu)

Operations Manager  
**Kathy Shores-Wilson, Ph.D.**  
214-648-4615 -- Tel  
877-757-3444 – Fax  
214-351-5119 – Hm  
214-657-9323 – Pager  
[kathy.shores-wilson@utsouthwestern.edu](mailto:kathy.shores-wilson@utsouthwestern.edu)



Administrative/Financial Manager

**Pat Blatney**

214-648-4604 - Tel

877-757-3444 – Fax

972-226-7139 – Hm

972-226-7139 - Hm Fax

800-946-4646 - Pin #1413013 - Pager

[pat.blatney@utsouthwestern.edu](mailto:pat.blatney@utsouthwestern.edu)

Communications Assistant

**Peggy Sherman-Daniels**

214-648-4623 – Tel

877-757-3444 – Fax

[stard@utsouthwestern.edu](mailto:stard@utsouthwestern.edu)

Star★D ROA Notification

877-798-3444

IVR Call-in Number

800-667-3315

IVR Technical Help

Diane Burroughs

800-316-2414, Ext. 2460

Data Coordinating Center Numbers

**Leslie Meloro**

412-624-1612

[melorol@edc.pitt.edu](mailto:melorol@edc.pitt.edu)

Brandi Lavrich

412-624-6016

[lavrighb@edc.pitt.edu](mailto:lavrighb@edc.pitt.edu)

**Andrew A. Nierenberg, M.D.**

Assistant STAR★D Safety Officer

Boston Special Function Regional Center

Massachusetts General Hospital

15 Parkman Street (WAC 812)

Boston, MA 02114

617-724-0837 – Tel

617-726-6768 – Fax

508-358-4163 – Hm

617-726-1818 – Pager

[anierenberg@partners.org](mailto:anierenberg@partners.org)

[oxbow@xensei.com](mailto:oxbow@xensei.com) – Hm email