Clinician Assessment Manual

RFP-NIH-NIMH 98-DS-0008

Treatment for Adolescents with Depression Study (TADS)

Final Version (4.0)

Principal Investigator: John S. March, MD, MPH, Duke University Medical Center and Duke Clinical Research Institute (DUMC/DCRI), P.O. Box 3001, Durham, NC 27710

Contact: John S. March, M.D.
Department of Child and Adolescent Psychiatry
Department of Psychology – Soc & HLTH
718 Rutherford St Durham, NC 27705
Box 3527 Med Ctr Durham, NC 27710
(p) 1-919-416-2404
(f) 1-919-416-2420
jsmarch@acpub.duke.edu

Adapted with permission from materials developed for ADHD clinical trials by C. Keith Conners, Ph.D., 1998, and from the IE Manual from the Treatment of Pediatric OCD Study (John March, Duke University, and Edna Foa, University of Pennsylvania, Co-Principal Investigators).

TABLE of CONTENTS

I. Overview

In a multi-site trial it is especially important to have common standards for the use of the CGI and other scales, or else widely divergent levels of severity and improvement could be represented at different sites due to different clinician standards for rating severity and change with treatment. Common standards for rating the main dependent measures are also necessary to insure that the same rater rating the same patient captures the initial status of the patient and subsequent changes with treatment accurately. By reducing unreliability between and within raters, the validity of the trial is protected from method variance in the application of rating scales with a consequent loss of study power.

To this end TADS will (1) follow five important principles and (2) implement specific guidelines for generating scores on the clinician-administered dependent measures. These principles are as follows:

First, when patients enter the study they must be of sufficient severity as indicated by a K-SADS diagnosis of MDD that is pervasive and stable and by an IE-administered CDRS-R Score $\geq$ 45 so that there is *room for improvement*. That is, if a patient is not impaired, then the treatment could not demonstrate any improvement that is clinically meaningful. Hence, unless that patient has made a notable improvement between the baseline assessment and treatment visit one, the initial CGI-S score must be at least moderately ill (CGI-S = 4) at the start of the study

Second, it is important to use more than one source of information (e.g. patient self-report, parent report and clinical observation) and to reconcile these sources to generate a valid and reliable summary judgment of the patient's clinical status with respect to severity of symptoms. Specifically, it is assumed that the clinician evaluator will have the benefit of (a) ongoing reports by the patient and the primary caretaker; and (b) direct observations during an interview with the patient and, typically, the primary caretaker. As in the case of severity judgments, the clinician must ultimately integrate information from the patient and parent report and direct interview into a final judgment of the degree of change noted in the patient.

Third, while it is possible to define severity solely in terms of a statistical criterion on a standardized rating scale, this is not entirely satisfactory because one can have severe *symptoms*, without having severe *impairment*. For example, a patient can be quite depressed, but have such a good environment and personal assets that depression causes relatively little impairment in functioning at home or school. (TADS requires that to enter the study a patient must show impaired function due to MDD in at least two of three domains: school, home, social relationships.) Hence, the CGI-S and CGI-I Scales include guidelines for rating the patient on specific impairment criteria.

Fourth, with both severity and improvement ratings, it is important to have some guidelines so that clinicians will use the scales in a similar fashion. This is accomplished by following a set of guidelines or algorithms as specified in this manual.

Fifth, the guideline must predict the dose of treatment within a clinically relevant stage of treatment framework, viz. informing dose escalation as a function of clinical status in Stage I and, if appropriate, Stage II. Dose of pharmacotherapy means number of milligrams of FLX and frequency of medication visits; dose for CBT means number and

frequency of sessions of CBT. This goal is met by using the CGI-S to drive treatment for partial responders in Stage I and II and in linking the medication and CBT interventions in combination treatment.

II. Clinician Qualifications

In addition to the qualifications that are specified in the CBT and Pharmacotherapy Manuals vis-à-vis readiness to provide clinical care in TADS, clinicians ideally should have experience administering research-related assessment tools, such as the K-SADS and CDRS-R. All clinicians will be required to review the CDRS-R manual, which provides detailed guidelines on interviewing depressed children and adolescents, especially Appendix A, which addresses the use of probe questions.

III. Procedures

Table 1: Clinician Dependent Measures

Measure	Respondent	When*	Assessment Domain
ADS	Patient	Office Visit	MDD, hypomania and mania
CGI-S	Patient and Parent	Office Visit	MDD-specific severity of illness
CGI-I	Patient and Parent	Office Visit	MDD-specific improvement
CGAS	Child and Parent	Office Visit	Global functioning

*Not including CBT parent-only visits or ASAP visits; office visit is defined as including phone visits as appropriate to study stage and treatment condition.

Every clinician (CBT therapist, pharmacotherapist or both, depending on whether the patient is in CBT, pills or COMB, respectively) will complete the clinician rating forms that are listed in Table One and described below:

- The Affective Disorder Screen (ADS), which is loosely modeled on the DSM-IV criteria sets for MDD and mania and on the CDRS and the Young Mania Rating Scale, guides the clinical review of affective symptoms at the beginning of each treatment session.
- The CGI-I and CGI-S assess MDD-specific degree of improvement or severity of illness at each office visit.
- The CGAS targets overall functioning, including impairments stemming from MDD as well as all other causes, e.g. co-morbidity or family problems.

Before each session, the clinician will review the previous week's assessments to be clear about target symptoms with respect to improvement from baseline.

Prior to meeting with the treating clinician, the ADS will be given to the patient by the study coordinator. The clinician will review the ADS with the patient and parent to reconcile any differences in reporting before assigning CGI scores.

At each office visit, the clinician will review the ADS and will obtain a CGI-S and CGI-I targeting MDD symptoms and a CGAS targeting overall functioning.

Having completed these ratings, the clinician may now move on to the remainder of the treatment visit.

Procedures for Patients in COMB

The patient is given only one instance of the ADS to complete before the visit starts, which is not a problem for patients in monotherapy conditions since they see only one doctor. However, in the COMB condition where it is expected that visits with the pharmacotherapist and CBT therapist will be back-to-back, the patient would then be subject to two full ADS reviews. To avoid this, the pharmacotherapist will see the patient first, score the ADS, and then pass the already scored ADS along to the CBT therapist who will quickly review the ADS without scoring a second iteration of the scale.

Note that a similar procedure obtains for adverse and concomitant medication/treatment recording, namely the pharmacotherapist in concert with the study coordinator will be responsible for recording adverse events and intercurrent treatments for patients in the COMB condition.

Instructions to the IE, Clinician and Patient/Parent Regarding IE Blinding

To insure that the IE remains blind, we will put the following safeguards in place:

- At the Gate C2 visit, the site team member who reveals randomization will inform the patient/parent that the IE will not know the patient's treatment assignment and that they (patient and parent) should not tell them. Furthermore, the patient/parent should be told that this is to minimize the chance that an IE will have a favorite treatment and, even without intending to do so, will give that treatment better scores.
- Immediately before each IE visit, the patient and parent will be reminded by the study coordinator not to telegraph or to declare their treatment assignment.
- Additionally, the IE Supervisor will remind the IE to be careful not to ask questions regarding the effect of treatment.
- To remove any sense of "coaching" the parent/patient regarding their responses to the IE, TADS clinicians (CBT and pharmacotherapist) will be instructed not to bring up or to discuss the IE battery.
- Ideally, the week 12 IE visit should come before the week 12 clinical visit where a determination is made regarding whether TADS Stage I treatment continues. If not, the clinician/SC will warn the patient not to reveal continuation status at this or subsequent IE visits. An analogous caution exists for all patients undergoing premature termination.
- QA procedures for the IE and Clinicians will include review procedures for insuring that the IE remains blind.

IV. Guidelines for Administering the ADS

The ADS contains 19 depression and 9 mania items that cover the major symptomatic and functional domains associated with major depression and mania, respectively. The ADS is first filled out by the patient, with input from the parent if present, and then reviewed by the clinician with patient and parent together at the beginning of each treatment visit.

The patient self-report portion of the ADS uses a dichotomous response metric (Symptom present, Yes/No). Based on input from the patient and the parent during the

clinical interview, the clinician will then score the ADS on a 0-3 point scale as absent, mild (present, no interference), moderate (present, some interference), or severe (present, major interference). This data will be transmitted to the CC for scoring.

When the patient and parent disagree, at the clinician's option, each can be interviewed separately, and then, when necessary, jointly to resolve differences in reporting. Ultimately, however, it is the clinician's judgment that must synthesize/reconcile all the available information into a summary judgment. Conversely, when the patient and parent do not disagree and the patient, parent and clinician are of the opinion that the patient report is sufficient, the parent interview can be treated as optional. When only the patient (or rarely, the parent) is present for the treatment visit, the clinician should score the ADS and other measures based on best clinical judgment. Note that the ADS is not to be given at parent-only CBT sessions.

Based on information gained from reviewing the ADS and a more general clinical interview, the clinician will assign a CGI-Improvement and CGI-Severity Score specifically targeting MDD symptoms.

Overview of Assessment Steps

Before reviewing the ADS, it is essential to review the baseline ADS (depression, mania and function items are scored separately) and CGI-S scores and the ADS and CGI-S scores from the previous weeks to place the current ratings in the context of the trajectory of change in MDD outcomes across study time. These ratings will be tabled and graphed at the front of each patient's chart and may be used with the patient to document the course of treatment.

As he/she reviews the ADS with the patient and parent, the clinician should go through the following steps to insure that the ADS score represents a reliable and valid understanding of the patient's symptoms.

Step 1: *Is the ADS a valid representation of depression for this particular patient?* Given an understanding of the patient's motivation to complete the scale, impact of co-morbidities on his/her ability to complete the scale accurately or with bias, the setting in which the ADS was administered, and the purpose for which the results will be used, the clinician must make a judgment regarding the validity of the ADS data. Motivational issues include the patient's desire to avoid treatment by inflating symptoms ("it is too hard; where's the magic pill") or minimizing symptoms ("I don't need it"). Concerns regarding self-presentation—for example, the need to look perfect in the eyes of valued adults—may introduce a systematic response bias, especially if the patient knows that a parent will see the results. This is a particular concern when a parent is required to help the patient read and/or understand the scale items. Not surprisingly, it is also important to consider whether response biases associated with the gender and/or cultural background might influence the patient's report of symptoms. As a first step then, it is important to inspect the pattern of item responses to see that they are internally consistent and consistent with the response patterns shown by other children of the same age, gender and race.

Step 2: *What is the overall level of affective symptomatology?* The ADS depression and mania subscale scores represent a measure of the overall level of depression and mania. Thus, while the ADS is not a normed instrument, an estimate of symptom severity can nonetheless be made by scanning the item scores for the depression and mania subscales to generate an item mean score. An item mean score of 0 indicates no to very minimal symptoms; an item mean score of 1 indicates mild symptoms; an item

mean score of 2 indicates moderate to moderately severe symptoms; and an item mean score approaching 3 indicates severe symptoms.

Step 3: *Are all items elevated or is there a pattern?* Examining the ADS depression and mania item scores should quickly allow the clinician to identify problem areas for mania versus depression.

Within depression, it is also important to examine symptom groupings as follows:

- Mood Items 1-6
- Vegetative symptoms Items 7-17
- Suicidality Item 18-19
- Interference with function Items 20-22

Mania items (23-31) follow immediately after the depression items.

Step 4: *What item responses are elevated?* Having obtained a good sense of the patient's global level of depression and mania and interference with functioning, it is now possible to scan the individual items for those that are or aren't particularly problematic. Particular items are very useful in helping the clinician target questions during the clinical interview and in selecting and following targets for treatment. Pay particular attention to the function-specific items 20 (school), 21 (friends) and 22 (family) as they become important in rating the CGI Severity and Improvement Scales and, especially, the CGAS which is strictly speaking a general function measure.

Step 5: *Integrate information from the ADS with other information.* Using available information from parent and patient interviews, the clinician can now interpret the ADS scores with respect to validity and clinical significance before going on to assign CGI-S, CGI-I and CGAS scores.

V. Guidelines for CGI Scores

A. Overview

Based on the ADS score and a clinically sensitive interview to ascertain the extent to which the subject experiences impairment due to MDD, the clinician should generate a best-estimate CGI-S and then CGI-I score, which should reflect the subject's current (over the past week) clinical status in light of the overall trajectory of change since baseline (T0).

Before interpreting the ADS score and assigning CGI-I and CGI-S and CGAS ratings, the clinician should review the previous scores since baseline, which will be available in table form at the front of the patient's clinical record.

The ADS score provides an estimation of deviance from normal that includes (implicitly and explicitly) the concept of associated impairment due to MDD symptoms. The guidelines that follow link the ADS score and the concepts of impairment and improvement as ascertained on the CGI-S and CGI-I scores across three domains of functioning (home, school and peers). Note the concept of impairment allows for the possibility of adequate functioning, c.f. "holding it together at school," despite the presence of significant MDD symptoms.

Because TADS is a study of treatments for MDD and these are the primary outcome measures for MDD in the study, **the clinician should be especially careful to focus on MDD only when composing CGI scores**. Other factors unrelated to MDD, such as

other externalizing or internalizing disorders, family functioning, neighborhood problems, difficulties at school, should not be considered. For example, when rating the CGI-S for a patient with an IQ of 80 who struggles in school, the IE should consider impact of struggling in school on MDD and, in turn, the impact of MDD on school performance, but the impact of a low IQ per se should not be considered when rating the CGI scores. Conversely, all factors that impinge on general functions, including but not limited to MDD, should be considered when ranking the CGAS.

B. Guidelines for making CGI-Severity Ratings.

The following guidelines link the ADS score and the concept of impairment across three domains of functioning (home, school and peers).

Discounting the not assessed category, the CGI-S is a 7 point scale anchored as follows:

GLOBAL SEVERITY

0= Not assessed	4= Moderately ill
1= Normal, not mentally ill	5= Markedly ill
2= Borderline mentally ill	6= Severely ill
3= Mildly ill	7= Extremely ill

It is assumed that the clinician will have the benefit of (a) direct observations during an interview with the patient, as well as a self-report regarding side effects and changes in symptoms; (b) other corroborative evidence, such as reports by significant others; and (c), previous ratings since baseline.

1. Normal, not mentally ill
    - Patient scores in the absent range (mostly zeros) on the ADS depression items
    - The patient is clinically in the normal range for depression symptoms
    - There is no impairment from MDD symptoms
2. Borderline mentally ill
    - Patient shows absent to mild symptoms (mostly scores of 0 and 1) on the ADS depression items
    - Patient does not meet diagnostic criteria for MDD
    - There is little or no impairment from MDD symptoms
3. Mildly Ill
    - Patient shows mild symptoms (average score of 1) on the ADS depression items
    - Patient does not meet diagnostic criteria for MDD
    - There is impairment in only one setting
4. Moderately Ill
    - Patient shows moderate symptoms (mostly scores of 1 and 2) on the ADS depression items
    - Patient meets diagnostic criteria for MDD

- There is impairment in two settings (home, school, social)

5. Markedly Ill
   - Patient shows moderate to moderately severe symptoms (average score 2+) on the ADS
   - Patient meets diagnostic criteria for MDD
   - There is impairment in two or three settings
6. Severely ill
   - Patient shows severe symptoms (mostly scores of 2 and 3) on the ADS depression items
   - Patient meets diagnostic criteria for MDD
   - There is clear impairment from MDD symptoms in 3 settings
7. Extremely ill
   - Patient is among the sickest MDD patients
   - Patient shows severe symptoms (mean score approaching 3) on the ADS
   - Patient meets diagnostic criteria for MDD
   - There is impairment in 3 settings

C. Guidelines for making CGI-Improvement Ratings.

As with the CGI-S, the CGI-I is also a 7 point scale anchored as follows:

GLOBAL IMPROVEMENT

0= Not assessed	4= No change
1= Very much improved	5= Slightly Worse
2= Much Improved	6= Much worse
3= Minimally improved	7= Very much worse

The following definitions of the CGI-I require an understanding of what constitutes a clinically significant improvement. **Since the CGI-I is always a judgment made in comparison to the patient's state at the start of the trial (baseline),** a *clinically significant* improvement is said to occur when the patient's symptoms move closer to normal functioning than to the patient's level at baseline.

When rating the CGI-I (as contrasted to the CGI-S, which is rated relative to an age, gender and community matched peer), the clinician asks the following question: compared to his/her condition at baseline, how much has he/she changed with respect to symptoms of major depression? Rate total improvement for major depression only whether or not, in your judgment, the improvement is entirely due to treatment.

1. Very Much Improved.
    - All or most of the target symptoms are reported by the patient as improved to a significant degree; that is, the changes have a major and discernible impact on functioning, both subjectively and as observed by others
    - Side effects from the treatment are minimal or non-existent
    - Symptomatic and functional status are such that the clinician would want to continue treating the patient on the same dosage of the treatment
    - There is little or no room for further improvement in depression
2. Much Improved
    - Several symptoms have improved to a degree that the patient feels an important change has occurred. The change may not be large enough that it is distinctly noticeable by other observers; some information may not fully confirm the changes
    - Some side effects may be present, but they are not significant enough by themselves to warrant changing the dosage of the treatment
    - There is still some room for improvement, but if necessary, this dosage of the treatment would still be considered very positive and possibly sufficient
3. Minimally Improved
    - Only 3 or 4 symptoms (at most) show improvement, and the degree of change is not sufficient that one would consider leaving the patient at that dose. There is no consistent improvement across informants or domains of function
    - Side effects may be present to a degree that maintenance at this dosage level is not indicated, even if a few desirable symptomatic or behavioral changes are evident
    - There is considerable room for improvement, clearly requiring further therapeutic adjustments
4. No Change
    - There are no symptoms that show improvement compared to the baseline state, or changes are so minimal as to be completely inconsequential
    - Side effects are not problematic
    - The patient's condition by self-report as well as by independent observations clearly indicate lack of desired benefits
5. Slightly Worse
    - There is some worsening over the baseline state in the target symptoms, though not to a degree that one would wish to completely stop treatment
    - There may be mild adverse effects that suggest the dosage is too high, such as side effects typically associated with high levels of this treatment
    - Although there may be positive changes, they are insufficient in comparison to the negative changes to consider staying at this dosage or with this treatment
    -

6. Much Worse
    - The patient's condition is worse enough that stopping or changing treatment is indicated, even though not all target symptoms are worse
    - There may be behavioral or physical side effects that are perceived as definitely uncomfortable or undesirable
    - Worsened condition is clearly discernible by the patient and other observers
7. Very Much Worse
    - Most of the target symptoms are worse; stopping treatment is indicated
    - Side effects may be intolerable or laboratory values may be definitely abnormal
    - The patient may spontaneously stop treatment due to adverse effects or worsened symptoms or more impaired functioning than at baseline

VI. CGAS

The Clinical Global Assessment Scale (CGAS), which will be completed after the ADS review and after generating the two CGI scores, is a measure of global functioning, not just functioning related to MDD. Unlike the CGI and CDRS scores, which are focused on major depression, the clinician should rate the CGAS relative to all areas of functioning, factoring in impairment from all sources, including all mental disorders, cognitive capacity, family and peer problems, SES and stressors. In addition, the clinician should rate the CGAS using the defined CGAS anchor points relative to age and gender matched peers, considering the baseline CGAS rating and change trajectory over the course of treatment.

VII. Summary

This manual presents guidelines for the clinician to use when rating the primary dependent measures. The CBT and Pharmacotherapy supervisors, working with the IE supervisor, should be familiar with the clinician manual and use it to supervise clinician ratings according to quality assurance procedures specified in the QA manual.