PROTOCOL

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Treatment for Adolescents with Depression Study (TADS)

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Table of Contents

Introduction

This protocol will organize, implement, and analyze the findings of a multicenter randomized trial to study the effectiveness of four treatments in adolescents with a DSM-IV diagnosis of major depression: cognitive behavior therapy (CBT), fluoxetine medication (FLX), combination of CBT and FLX (COMB), and pill placebo (PBO).

1.1. Background: Importance of the Trial

At any one time, about 1 in 20 children and adolescents suffers from major depressive disorder (MDD). Though the exact prevalence is controversial,[1] a smaller number, perhaps 1 in 200, suffers from bipolar affective disorder (BPAD), especially bipolar II and cyclothymia. Rates of depression rise dramatically in adolescents, with a pronounced gender effect: the point prevalence of depression is roughly equal in boys and girls in early adolescence; by age 14 the incidence of MDD in girls rapidly begins to exceed that for boys.[2] Many if not most depressed adolescents suffer from more than one disorder, more commonly externalizing in boys and internalizing in girls.[3] Chronic waxing and waning depressive symptoms are also common[4,5] and when remission of MDD occurs, relapse rates are relatively high.[2] Preliminary evidence suggests that MDD may be increasing in the pediatric population in a cohort fashion[6] and that childhood-onset anxiety or depressive disorders powerfully predict adult anxiety and depressive disorders.[7] Taken together, these findings indicate that affective illness in children and adolescents is prevalent, of significant public health importance, and thus a prime candidate for innovation in treatment.[8]

Costs Associated with MDD in Adolescents

While the economic burden of depression in youth is uncertain, the total cost associated with depression across the life span is in the tens of billions of dollars,[9] with the use of all medical services, not simply psychiatric services, increasing dramatically.[10] In a recent review of findings from a number of studies in adults, Wells, et. al.,[11] noted that the indirect costs of affective disorders, such as reduced productivity of the depressed person and increased burden on family members, far exceed the direct costs of treatment. Similar findings are present in children and adolescents perhaps because young persons are even less likely than adults to receive competent mental health services.[12] Given the substantial burden on the family imposed by mental illness in a teenager,[13] the human costs may be even greater than the economic costs. Of these costs, none is greater than teenage suicide. While the population prevalence of suicide in the context of depression is unknown, affective illness (especially bipolar disorder) is a principal risk factor for suicide attempts among teenagers, and even more, for completed suicide.[14] Consequently, improvements in the treatment of adolescent depression would have both a strong public health impact and an important economic impact.

The Treatment Literature Warrants a Multicenter Randomized Clinical Trial (RCT)

The empirical literature on treating pediatric major depression is somewhat more supportive for problem-specific psychotherapies than for medication management.[8,15,16] Several controlled trials have now shown that individual or group-administered cognitive-behavioral psychotherapy is an effective treatment for depressed children and adolescents.[17,18] A recent meta-analysis of 6 controlled cognitive behavioral therapy (CBT) studies in depressed adolescents yielded a reasonably robust overall post-treatment effect size of 1.02, whereas the overall effect size at follow-up was 0.61.[16] Thus, it seems appropriate at this juncture to extend and replicate the studies favoring CBT as a treatment for adolescent major depression in a more diverse patient sample, with greater reliance on tracking long-term outcome across domains beyond the purely symptomatic.[15,19]

In contrast to the literature on CBT, the empirical literature on psychopharmacological interventions in pediatric MDD is not entirely convincing with respect to efficacy.[20] Apart from a single controlled trial in which fluoxetine proved more effective than pill placebo in depressed children and adolescents,[21] there are no published controlled trials to support the use of pharmacotherapies in this patient population. A recent still unpublished multicenter placebo-controlled study of paroxetine vs. imipramine

also shows benefit for paroxetine (a selective serotonin reuptake inhibitor, or SSRI), but not for the active comparator (imipramine). (Graham Emslie, NCDEU, 1999). Amazingly, more than a dozen negative RCTs using various tricyclic antidepressants (TCAs) have now been conducted,[20,22,23] essentially ruling out the TCAs in a study such as the one proposed here. Conversely, because the SSRIs are widely used as first-line treatments for depressed youth,[24] it is critical that the study by Emslie and colleagues be rapidly replicated in a larger population of adolescents, which constitute by far the largest group of young persons with major depression. Additionally, because a substantial proportion of the Emslie sample relapsed during the first year of follow-up off medication,[25] extension of this study with longer-term drug treatment is essential. Parenthetically, there is no intention to use TADS as a registration trial and the FDA has granted TADS an exemption from filing an investigational new drug application (IND).

Although the relative efficacy of CBT, and medication alone and in combination, remains uncertain, most clinicians recommend combined treatment as the treatment of choice for MDD in the pediatric population.[20] In fact, if results in adults[26] hold true for adolescents, the combination of CBT and medication may well lead to more durable symptom remission in depressed patients than monotherapy with either treatment alone. Thus, as pointed out by NIMH program staff,[24,27] well-designed comparative treatment outcome studies in the same patient population are necessary to determine the relative advantages and disadvantages of these treatments.[19]

Lessons from the Treatment of Depression Collaborative Research Program

While it is not possible to directly translate the results of studies in adults to children and adolescents, witness the lack of efficacy for TCAs in the pediatric population, there are some useful lessons to be drawn from the NIMH Treatment of Depression Collaborative Research Program,[28] which contrasted interpersonal psychotherapy (IPT), cognitive behavior therapy, imipramine hydrochloride (IMI) plus clinical management (as a standard reference treatment), and placebo plus clinical management. In the TDCRP, all patients improved, with IMI and IPT showing more benefit, particularly among the more severely depressed patients, where IMI was the superior treatment.[29] This study has generated numerous subanalyses,[30-32] with particular attention to the use of more sophisticated random regression techniques.[33] In the proposed study, we (1) emphasize obtaining a sample of clinically ill teenagers showing stable clinically-relevant dysphoria, and (2) use the most sophisticated available data analytic methods to track rigorously assessed main and secondary outcomes, as well as moderator and mediator effects.

Translating Research to Clinical Practice

To quickly translate the fruits of research to clinical practice, pediatric psychiatry/psychology requires a pronounced shift to a more evidenced-based practice standard, sometimes termed evidence-based medicine (EBM).[34-36] EBM de-emphasizes the all-too-typical reliance on unsystematic clinical experience as a sufficient ground for clinical decision-making, and stresses instead the examination of evidence from systematic diagnostic assessment technologies and clinical research as tools to inform clinical practice. It provides a heuristically valuable organizing focus for the individual clinician seeking to transition efficacy and effectiveness studies into clinical practice.[37] It is especially important that evidence-based practice guidelines be developed in the context of a stages-of-treatment model that includes maintenance and discontinuation stages.[38,39] In this study, we have maximized the strength of the evidence for treatment efficacy where possible (e.g., by relying on randomization) while at the same time testing treatments that have potential for real-world application in a stages-of-treatment model.

Effectiveness Trials Can Have an Impact on Economic Cost of Treatment

If the relative effectiveness of long-term treatments for MDD could be more definitively established, it would boost the chances that state-of-the-art care for depressed adolescents would become a standardized therapeutic option in the U.S. for a disorder that is common, disabling, costly, associated with substantial morbidity and mortality, and not always easy to treat.[20] Such a development would have important implications for health economics. The restructuring in the U.S. health service delivery system over the past decade, particularly with respect to financing and use-control mechanisms, has

focused renewed attention on costs associated with various treatments.[40] In 1992, the estimated retail cost of 6 months of antidepressant therapy with fluoxetine varied from $327 to $1,310 depending on dosage level.[41] By contrast, the estimated retail cost of 6 months CBT as proposed herein is about $2,600. Thus, there may be a considerable cost advantage in favor of drug treatment, if it can be shown to have comparable efficacy and, most importantly, durability, since costs rise dramatically when prolonged treatment is required. Conversely, if CBT or combination treatment were to show greater short-term efficacy and/or long-term durability, then they would likely prove more cost-effective in the long run despite higher short-term costs . Answers to questions such as these are critical, given the Zeitgeist of managed care and other efforts to reduce the cost of health care in the U.S.

1.2. Summary

In summary, this study stands at the confluence of current efforts to improve the treatment of adolescent depression and related outcomes. Combined with other similar studies, for example, the Multimodal Treatment of ADHD (MTA) study, it represents an important building block in efforts to assemble a comprehensive public health approach to the treatment of pediatric mental illness in the U.S. and elsewhere.

2. Study Design

The Treatment for Adolescents with Depression Study (TADS) is a multicenter randomized clinical trial examining the comparative effectiveness of established treatments for adolescents with major depressive disorder (MDD). TADS will use a volunteer sample of 432 youth (48 subjects/site x 9 sites) age 12-17 inclusive with a DSM-IV diagnosis of MDD to contrast the degree and durability of improvement obtained across four treatment strategies: fluoxetine alone (FLX), MDD-specific cognitive-behavior therapy (CBT), both FLX and CBT (COMB), and a single control condition, pill placebo.

2.1. Specific Aims

The RFP called for a large heterogeneous sample of patients to see if treatment results in sustained improvement in symptoms and level of functioning in patients representative of those found in clinical practice. The specific research objectives were clearly spelled out in amendment 1 to the RFP. a) What is the long-term effectiveness of pharmacological treatment of adolescents with major depression? What is the impact of treatment on symptom reduction, disorder remission, and level of functioning in school, at home, or in the community, and on the use of auxiliary services? (b) What is the long-term effectiveness of specific psychotherapy (e.g., cognitive-behavioral therapy) in the treatment of major depression in adolescents with major depression? What is the impact of the treatment on symptom reduction, disorder remission, and level of functioning in school, at home, or in the community, and on the use of auxiliary services? (c) How do these pharmacological and psychotherapeutic treatments compare with each other in terms of effectiveness, tolerability, and adolescent and family acceptance? (d) Will adolescents who are not responsive to one treatment approach (either pharmacotherapy or psychotherapy) respond to the other treatment approach? (e) What is the cost-effectiveness of medication, psychotherapy, and combined treatments? With the exception of aim (d), which proved unfeasible from a cost point-of-view, TADS meets each of the aims articulated in the RFP. The final TADS design provides answers to each of these research objectives except the fourth, which was not feasible within the constraints of the remaining scientific goals espoused in the RFP.

The two primary questions addressed by TADS involve, first, an acute comparison of three study-delivered treatments (medication, psychotherapy and their combination) against a PBO control condition and, second, a longer term comparison of the three study-delivered treatments to each other.

With respect to treatment composition, there are four stages that represent high standard evidence-based treatments seen in clinical practice:

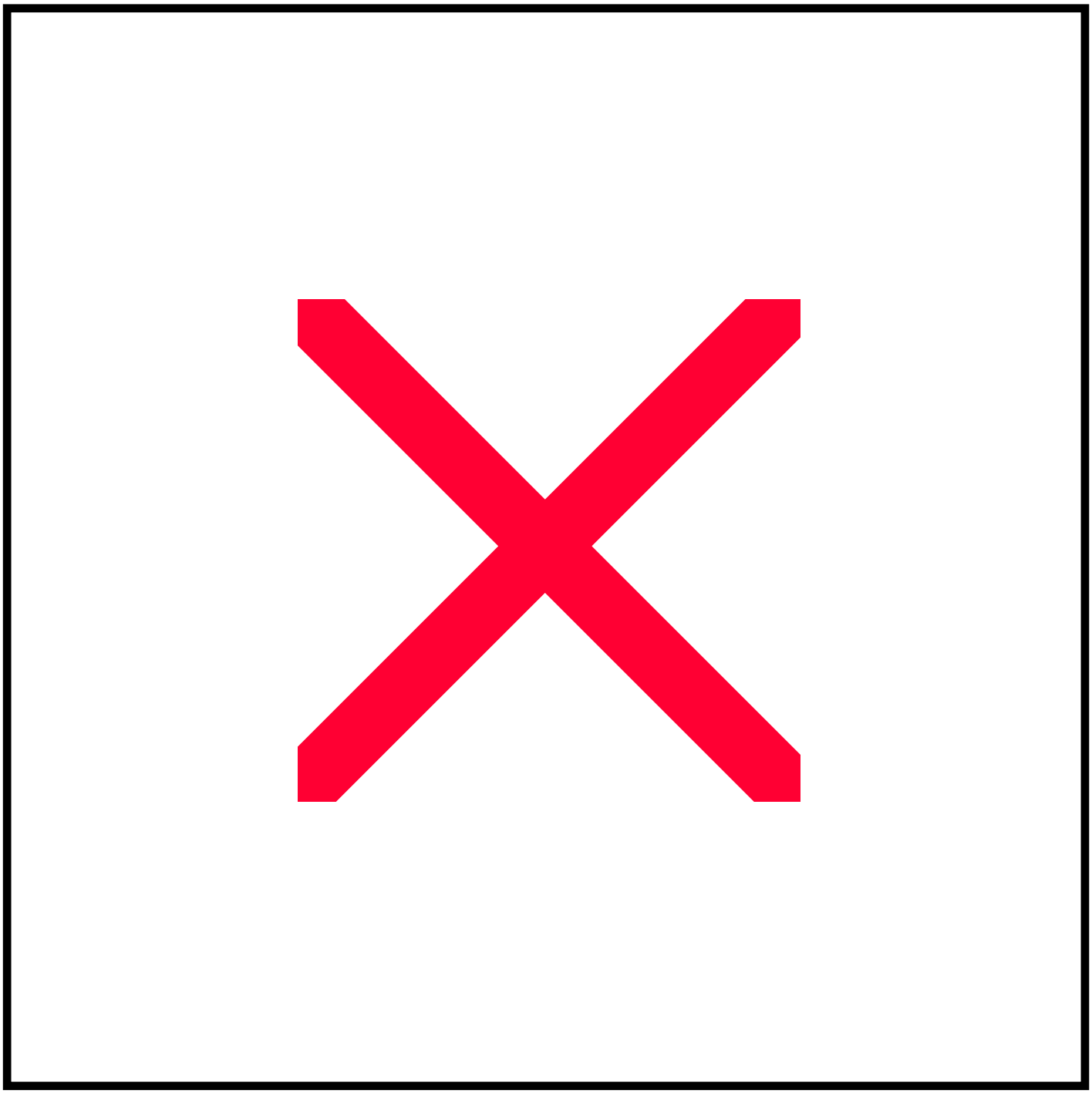
- Stage I represents acute treatment after which a judgment can be made about whether a particular treatment is worth continuing and at what intensity.

- Stage II consolidates treatment gains for responders and provides additional intensive treatment for partial responders.
- To reduce the risk of early relapse, Stage III provides longer-term maintenance treatment.
- Stage IV represents a one-year period of open follow-up to monitor for relapse once treatment has been discontinued.

With respect to duration, the four TADS treatment stages provide: (1) 12 weeks of acute treatment, (2) six weeks of early maintenance and consolidation of treatment, (3) 18 weeks of long-term maintenance treatment, for a total duration of active treatment of 36 weeks, and (4) 1 year of open follow-up.

Our specific aims are as follows:

1. To compare the effectiveness of FLX, CBT, COMB, and PBO for reducing MDD symptoms and patient disability acutely.
2. To compare the effectiveness of the three active treatments (FLX, CBT, and COMB) during long-term treatment.
3. To compare the acute time-action profiles (speed of response) of FLX, CBT and COMB.
4. To compare relapse rates, MDD-associated impairment and use of mental health/medical services for FLX, CBT and COMB during long-term maintenance treatment and during open follow-up.
5. To explore predictors of response to treatment, including initial severity, comorbid internalizing and externalizing symptoms, treatment expectations, and family psychopathology and functioning.
6. To examine the long-term acceptability and cost effectiveness of FLX, CBT and COMB for the treatment of MDD in adolescents.



2.2. Hypotheses

TADS includes major assessments (full assessment battery) at baseline, 12 weeks, 24 weeks and 36 weeks, with minor assessments (reduced assessment battery) at 6 weeks, 18 weeks and 30 weeks. For each assessment point, major or minor, we obtain all the "primary outcome" measures as rated by an independent evaluator (IE). Finally, during the Stage IV open follow-up, we obtain major assessments at 6 and 12 months and minor assessments at 3 and 9 months.

Table 1 states the primary and secondary hypotheses by time, acute and long term. The acute comparison is represented by Stage I and includes PBO-treated patients. The long-term comparison includes Stages I, II and III, namely the entirety of the randomized portion of the trial, and includes only the three active treatments.

Table 1: Hypotheses

Hypothesis[1]	Type[2]	Acute[3]	Long-term
Subjects in each of the three active treatment groups (medication, CBT, combined) will show more improvement on measures of major depression than those assigned to PBO.	P	X	
Subjects assigned to the combined treatment group will show more improvement on measures of major depression than those assigned to the CBT-only or medication-only groups.	P	X	X
Subjects in each of the three active treatment groups (medication, CBT, combined) will show higher levels of overall improvement and overall functioning than those assigned to the PBO group.	S	X	
Subjects assigned to the combined treatment group will show higher levels of overall improvement and overall functioning than those assigned to either the medication-only group or the CBT-only group.	S	X	X
Subjects assigned to the combined treatment group will improve more rapidly than those assigned to either the CBT only or medication-only groups.	S	X	X
Consumer satisfaction and long-term cost effectiveness will be greater for the combined than for the CBT-only or medication-only groups	S	X	X
In Stage IV open F/U, subjects in the combined group will show greater improvement, lower relapse rates and more appropriate use of health services than CBT-only or medication-only treated patients	S		X

[1]No hypotheses are presented for CBT vs. FLX.

[2]P= primary hypotheses involve changes in MDD for which the study is powered; S = secondary; while critical to the scientific goals of TADS, secondary hypotheses are considered exploratory since TADS is not powered to test these hypotheses.

[3]Acute = Stage I; Long-term = Stage I, II and III, but not Stage IV

2.2.1. Commentary on Design Issues

In proposing an experimental design and developing a protocol to implement it, we confronted a variety of difficult design choices that we believe merit additional comment.

Stage I

Stage I is a randomized comparison of the four study treatments alone and in combination across all important outcome domains. This study replicates and extends previous efficacy studies with both CBT and FLX. Randomized contrasting group studies are essential to establish the causal nature of the relationship between the IV (treatments) and the DV (outcome domains) because randomization controls for many of the most important threats to the internal validity of the study.[42-44] In terms of the general linear model of prediction, these studies permit the greatest confidence that the hypothesized treatment is the only salient difference between the two groups, and, thus, is the reason for any detected differences in outcome.[45] In this regard, both sequential and simultaneous research strategies have been

used in treatment outcome studies to test the efficacy of treatments for the same disorder. A sequential strategy contrasts each active treatment in a parallel group trial against an appropriately chosen control condition. Then, active treatments are contrasted against each other in a second controlled trial, which can be either one-way or factorial in design. While factorial designs use fewer subjects with greater power, they also require cells devoted to treatment combinations (such as PBO plus CBT) that do not exist in nature as well as needing a no treatment control or controls for both psychosocial and medication treatments.[46] Hence factorial designs are better suited to strict efficacy as contrasted to effectiveness studies like the one proposed herein, which properly aims to contrast treatments as they are implemented in clinical practice.[37] Since treatments are tested in the same subject population, a study like this one also yields important results even if the active treatments prove equally effective in comparison to the control condition for the following reasons: (1) costs vary considerably between treatments; (2) expert CBT is less widely available than medications; and (3), subgroups of patients (identified on analyses of predictor variables) might preferentially benefit or not benefit from a particular treatment strategy.

Pill placebo control condition

Most investigators believe that control conditions, which are essential to controlling for (1) the demand characteristics of the active treatments and (2) for spontaneous remission,[47,48] are an especially critical consideration in studies of pediatric MDD where PBO response rates (in pharmacological studies) vary from 1/3 to 2/3 of the sample.[19,49] In this study, we believe that an inactive control condition is essential to making causal attributions about the differential effectiveness of treatment groups. Succinctly stated, the primary purpose of the trial is to evaluate the comparative efficacy of the three active treatments; however, if the three active treatments cannot be shown to be better than PBO, it will not be possible to differentiate between the failure of the trial or the failure of the treatments. In this regard, we discarded the fully factorial 2 x 2 design because (among other reasons) the control condition required randomization to no treatment (unethical and unfeasible) or to a combination pill PBO/psychosocial control (unfeasible and unreasonable in an effectiveness study). Instead, we propose to use pill placebo as the control condition for all three active treatments acknowledging that doing so is controversial. For an insightful discussion of these issues, which are beyond the reach of this proposal to discuss, see the work of Arnold,[50] Jacobson,[42,43] and Klein.[51]

In Gene Arnold's apt wording,[50] choosing a control condition boils down to answering the question: "Controlling for what?" which we answer in five parts. First, given that we remove the contributions of rater expectancy by using independent evaluators, the point of the control condition is to make the patients "think" that they are getting active treatment, to gauge the effect of positive pro-active engagement behavior on the part of the treating clinician and expectancy effects on the part of patients. Since it provides "faith" in treatment, PBO meets this test. Second, in contrast to placebo, which by definition cannot contain any unsuspected active factors, any psychosocial procedure that "mimics" clinically appropriate CBT for MDD would confound the internal validity of the experimental design. Stated differently, sham psychosocial treatments lack credibility; credible psychosocial controls are likely active treatments that attenuate the ability to find between-group differences.[52] Even if an acceptable sham CBT treatment were available, the cost of providing sham CBT in this study would be prohibitive. Third, since the test of COMB treatment relative to FLX and CBT is among the more interesting contrasts, the choice of control is to some extent determined by the need to control for COMB treatment. This necessitates inclusion of a PBO component. Fourth, although the amount of contact time will differ between treatment groups, with FLX = PBO < CBT < COMB, these experimental differences match real world treatment patterns and so contribute to generalizability. Fifth, therapist allegiance and competence is matched to treatments (and also measured) thereby removing potential artifacts associated with therapist expectancy and training.[43] Finally, even if scientifically unequivocal causal attributions regarding treatment comparisons cannot be made using pill PBO as the control condition, pragmatic considerations are more important with respect to interpreting the outcome of what is by choice an effectiveness study. For example, if CBT is superior to PBO, the utility of treatment over non-treatment likely is also shown; if CBT is no better than PBO, then it would be

important clinically to know that this treatment cannot beat pill-placebo case management. Taken as a whole, we find these arguments make a persuasive case for PBO as the control condition in this effectiveness study.

Given that we choose a PBO control condition, we have to come to terms with the high PBO response rate (ranging from ~30-60%) in previous studies of pediatric MDD and its consequent adverse effects on power. Let us assume that (1) spontaneous remission, (2) the demand characteristics of the treatments, and (3) method variance in assessment procedures (for example, regression to the mean) account for most of the variance in the dependent variable associated with the "placebo response."

When considering spontaneous remission, it is helpful to separate remission into early (e.g., during recruitment or early in treatment) and late remission (later in treatment). Taking early remission first, it is important to note that depressed adolescents vary considerably in mood state from week to week.[53] Besides the fact that a PBO run-in is an unsuitable antecedent for the CBT condition, this short-term baseline instability also makes a PBO run-in unsatisfactory as a method for identifying "placebo responders." Rather the goal should be stable dysphoria at randomization. Based on their experience recruiting subjects for medication treatment study,[54] Emslie's group suggests that "(1) subjects should not be excluded from randomized controlled clinical treatment trials based solely on improvement of symptom severity between visits, and (2) an extended evaluation period is warranted, especially for adolescents whose symptom severity tends to fluctuate from week to week."[54] Hence, following Emslie's lead (personal communication), we have elected to use an extended evaluation period to recruit and later randomize subjects with a stable and pervasive dysphoric baseline.

With respect to late remission, Lewinsohn and colleagues found in a population sample of adolescents that MDD episode duration ranges widely from 2 to 520 weeks, with a mean of 26.4 weeks (SE = 3.3) and a median of 8.0 weeks. Longer episodes were observed in those whose depression occurred early (at or before age 15), whose depression had been accompanied by suicidal ideation, and for whom treatment was sought.[55] To minimize the rate of spontaneous remission associated with entry into the study near the end of the index episode of MDD, one option would be to include time from onset to randomization as an entry criterion, excluding long-duration illness, say cases that are more than 4 months from onset. However, given the variability of episode duration, our inability to predict remission, and the adverse impact on external validity (generalization), this strategy seems both impractical and scientifically unwarranted. Instead, we choose again to rely on an entry procedure that guarantees stable dysphoria at randomization and to treat length of episode at study entry as a potential moderator of treatment outcome.

Addressing the demand characteristics of treatments is a much easier task. As discussed below**,** we provide comprehensive training to psychosocial and pharmacotherapists to ensure that demand characteristics other than those that intrinsically differ between the treatments are equated across the treatment groups. Given the likelihood that clinician contact and frequent assessments in research studies contribute substantially to demand characteristics, we also pay particular attention to minimizing the non-specific effects of treatment that are not characteristic of good medical practice.

With respect to minimizing instability in the assessment/measurement model, we have chosen measures offering the highest possible validity and, especially, test-retest reliability; used an independent evaluator trained and monitored to a prespecified criterion; and employed state of the art statistical procedures, including random regression (e.g., HLM, multilevel modeling), to minimize risks to the internal validity of the study associated with the inclusion of a PBO cell.

Nonetheless, while we derived our PBO response estimate from the fluoxetine study of Emslie and colleagues, where 56% of those receiving fluoxetine and only 33% of those receiving placebo were rated "much" or "very much" improved on the Clinical Global Impressions scale in the intent-to-treat sample,[56] no one can be sure that the proposed methodological strategies, which go beyond those of Emslie and colleagues, will work as advertised even though they represent the state of the art in this area.

Duration of PBO Control Condition

A related question is "How long to follow patients on blinded PBO treatment?" While the PBO control group is an essential design feature in Stage I, beyond Stage I there are advantages and disadvantages to continuing to blindly treat subjects randomized initially to PBO.

Among the advantages: First, if all subjects were to stay in treatment, keeping randomization intact provides ongoing control for the demand characteristics of study-delivered treatments and allows exploration of predictors of long-term PBO response. Second, in its purest form, continuing the PBO arm avoids the cost of treating PBO subjects, since responders continue and non-responders move to community treatment. On the other hand, it is highly likely that most of not all site IRBs will require us to offer treatment to non-responder and relapsing subjects assigned to PBO.

Among the disadvantages: Most importantly, long term PBO treatment lacks ecological validity. Hence, whether PBO is effective over the long term, and what predicts this phenomenon, is necessarily a secondary question not specified in the RFP. Including a long term PBO as contrasted to unblinding the PBO and then providing open treatment would make recruitment more difficult. While all IRBs will accept short-term PBO treatment, long-term PBO treatment may be a more difficult problem, especially when considering how to treat marginal responders. If the medication arm remains blinded, all medication treated patients, including FLX treated patients, enter consolidation and maintenance treatment without knowing whether or not they are on active medication. Because cognitive attributions regarding the benefit of treatment may be related to outcome, this potentially attenuates the ecological validity of the follow-up comparison of medication and CBT, since the latter clearly know that they are receiving an active treatment. Furthermore, in marginal responders or during a transient crisis, the tendency to drop a medication-treated subject to "find out" whether he/she is on PBO or FLX will be difficult to resist and may result in unwarranted subject attrition and site by treatment interactions.

Considered jointly, there is a compelling rationale for unblinding the PBO/FLX (pills only) condition at the end of 12 weeks, which will in turn attenuate interest in the long-term treatment of the PBO responders. Thus, PBO treated subjects will be treated openly and will return for full but not reduced assessments during Stages II-IV.

Stage II

The randomized clinical trial (RCT) is clearly the "gold standard" in both efficacy and effectiveness research.[57] However, not all questions can be addressed in the framework of an RCT, emphasizing the need for innovative approaches to treatment outcome studies that take into consideration the strength of the evidence so that useful data are not "wasted." Such an approach is especially crucial in long-term effectiveness research where the protection from confounding variables at baseline is often lost as patients proceed through the clinical trial.[58,59]

In this instance, we faced the clinically relevant requirement to solidify Stage I treatment gains in subjects emerging as responders in Stage I and to provide additional intensive treatment to partial responders. The latter is critically important as further brief treatment may obliterate differences between COMB and monotherapy conditions hypothesized at the end of Stage I, with great importance for cost analyses. Hence, Stage II implements a treatment extension design in which nonresponders to any treatment at the end of Stage I now advance to open community treatment, or for ethical and practical reasons in the case of PBO, to open treatment given by the study team. Responders at the end of Stage I advance to 6 weeks of reduced intensity consolidation treatment in their assigned arm. Partial responders to CBT or COMB receive an additional 6 weeks of CBT in their assigned arm. For partial responders to FLX or COMB, the dosing schedule for FLX allows flexible upward titration to a maximum of 60 mg.

The primary alternative to Stage II as presently constituted is a treatment addition study in which it would have been necessary to continue Stage I nonresponders on their Stage I treatment while randomizing to active and control conditions for the new treatment, e.g., to randomize the CBT

nonresponder group to CBT + FLX or CBT + PBO. In the FLX nonresponder group, subjects would have to have been randomized to FLX + CBT or FLX plus a psychosocial control condition. We elected not to pursue this path for several reasons. First and most important, too few subjects would have been available to adequately power re-randomizing Stage I nonresponders to the new treatments. Stated differently, sacrificing the interesting and clinically important contrasts provided by the Stage I COMB and PBO groups leaving more subjects in CBT and FLX alone to power the treatment addition study seemed unwarranted, given the overall goals of the RFP. Second, we did not wish to devote scarce resources to developing and implementing a psychosocial control condition. Third, our effectiveness study design intentionally resembles clinical experience. In this context, the potential biases introduced into subject recruitment (and therefore generalizability) by re-randomizing subjects at Stage II exceeded in our judgment the benefits to be gained by controlling for history effects. Lastly, we believe that it is first necessary to replicate and extend the basic efficacy studies using PBO control before advancing to a two-group discontinuation design.

Stages III and IV

Acute monotherapy treatment studies in pediatric MDD suggest failure rates ranging from 30 to 60%[8,60], hence the rationale for long-term treatment as proposed for this study. Similarly, follow-up studies of children and adolescents with anxiety and depressive disorders have consistently documented the continuation of significant problems into adolescence and early adulthood.[7] In the study by Lewinsohn,[55] of the adolescents who recovered, 5% relapsed within 6 months, 12% relapsed within 1 year, and about 33% relapsed within 4 years. Preliminary data suggest that relapse rates are much higher in clinically treated samples, with the probability of relapse greatest in the first six to twelve months after treatment ends.[21,61] A similar conclusion is suggested by the fact that the effect size of CBT for MDD decreased from about 1 at post-treatment to 0.6 at follow-up.[16] In the Brent, et al.[17] study of individual CBT, 40% of subjects relapsed at 1 year post-treatment (Boris Birmaher, personal communication). In the Emslie FLX study,[56] which included both children and adolescents, naturalistic follow-up revealed that 39% of those who recovered (some medicated, some not) had a recurrence of depression, with 55% of relapses occurring within 6 months.[25] In this study,[25] maintenance of treatment gains was associated with younger age, lower severity of depressive symptoms, higher family functioning, and fewer comorbid diagnoses. Poor family functioning was a major predictor of relapse in the Brent sample as well (Boris Birmaher, personal communication), suggesting that targeting poor family functioning in CBT condition may differentially mediate outcome in a positive direction. Given these high recurrence rates, we chose to continue treatment on a reduced scale for an additional 18 weeks in Stage III (for a total duration of active treatment of 36 weeks) in order to approximate whether the initial efficacy can be maintained over time.

In Stage IV, where patients are followed openly for an additional 52 weeks, we ask whether there are differences across treatment groups in durability of treatment gains once study delivered treatment is discontinued. Differential effects of outcomes other than MDD, including resource use and moderators and mediators of treatment outcome and of relapse, are among the many important questions that can be addressed in Stages III and IV.

Before arriving at the four stage design enumerated above, we initially proposed a Stage III randomized double-blind placebo-controlled discontinuation trial for all treatment responders who happened to have been medicated at the end of Stage II. Such a design measures in a controlled fashion the effectiveness of continued active medication as well as possibly shedding some light on the nature of the PBO response. In a recent placebo substitution study of fluoxetine in adults with MDD,[62] the investigators hypothesized that prolonged persistent ("true drug") improvement would be associated with antidepressant medication whereas early non-persistent ("placebo") benefit would be more typical of a placebo response. Thus, responders on active drug should do best if they continue to receive active drug and responders with a placebo-like response should have an equivalent prognosis whether they continued to receive the drug or were switched to placebo at post-treatment. They found that patients with a true drug response pattern relapsed significantly more frequently if they were switched to placebo than if they continued to receive fluoxetine. Patients with a placebo response pattern had an equivalent

outcome whether maintained on fluoxetine therapy or placebo. Patients with a placebo response pattern also relapsed more often when they continued to receive fluoxetine than patients with a true drug response pattern. While replicating and extending these results in this study via examining differential relapse by CBT status, e.g., as an unbalanced 9 (site) x 2 (CBT) x 2 (FLX/PBO) factorial PBO substitution trial, would have been of considerable interest, the additional complexity and two studies already in the field with FLX/PBO substitution components, made this design less attractive.

We also considered and discarded an active maintenance follow-up in lieu of the three phase design, viz. to eliminate Stage III by extending and modifying Stage II. The goal of an active maintenance follow-up is to enhance or at least preserve treatment effects, through some form of low-intensity booster treatment. This added treatment would afford the opportunity to study truly long-term treatment effects and perhaps to estimate a minimum time for cost-effective treatment through various discontinuation procedures. One possible design we considered was to deliver maintenance therapy within the context of a treatment-extension design, wherein booster sessions in the assigned treatment are provided to all participants in the 3 active treatment arms as a hypothesized means of enhancing long-term treatment effectiveness. This procedure would have the advantages of enhancing sample rapport, maintaining better control of the sample, insuring that the original random assignment is preserved, and preserving power for an extension of the original primary hypotheses, as well as studying the effects of truly long-term treatment. Alternatively, rather than merely extend the assigned treatment, we considered evaluating the effectiveness of maintenance therapy via random assignment to maintenance treatment: we could randomize the participants (stratified by treatment arm) at the end of Stage II to 2 groups, each of which would either receive or not receive maintenance booster sessions. A variation of this design would have been to randomize patients to increasingly longer maintenance baselines. This type of approach has great appeal, possibly deriving valuable additional knowledge about the necessary length of treatment and the feasibility of maintenance or booster sessions. However, notwithstanding the attractiveness of such possible active-maintenance-treatment designs, a host of scientific, methodological, clinical, and financial factors argued against an active-maintenance follow-up Stage,[63] and as a result we did not propose this option.

A Community Treatment as Usual Comparison Group?

Lastly, we considered and discarded a community-based treatment as usual comparison condition, termed an assessment and referral (A/R) group In this design, the long-term comparison of the three study-delivered treatments against A/R generated a primary question that was not part of the RFP, but which carried considerable public health interest. In this design, Stage I employed a 12-week 1 x 5 comparison of CBT, FLX, COMB, PBO and A/R. Stage II became a 6-week 1 x 4 variable intensity maintenance/consolidation phase. Similarly, Stage III was an 18-week 1 x 4 lower intensity maintenance phase. As with the final design, the total duration of treatment was 36 weeks (nine 4-week blocks) followed by a one-year open follow-up period.

The advantages of including an A/R condition were considerable. While not part of the RFP, it is clear that the public health impact of TADS would be strengthened if study-delivered treatments separate from community treatment as usual, much as has been the case in the MTA study. Reflecting the public health imperative, the A/R group permitted us to estimate not only the relative efficacy but also the functional and cost advantages of high quality well delivered treatments compared to community standard care . At the point when TADS reaches the publication stage, it is likely that the scientific literature in this area would warrant a broad based long term effectiveness study that contrasts evidence-based treatment with community standard care. Thus, for reasons of cost and timeliness, an A/R group in TADS appeared warranted. Including an A/R group also would have allowed us to anticipate whether dissemination strategies are warranted. Stated differently, if well-delivered study treatments proved better than A/R, then dissemination trials in which the unit of randomization is a service delivery system rather than individual patients would be a next logical research step.

Ultimately, though, these not inconsiderable advantages were outweighed by important disadvantages. With both A/R and PBO arms, two fifths of the subjects would receive a potentially "less desirable"

treatment, which might have adverse effects on recruitment. Even if the means separated, the SD in the A/R group would likely have been substantially larger than in study-delivered treatments, with unpredictable effects on the power to find between-group differences. Hence, power likely would have been substantially weaker for comparisons involving the A/R group and site by treatment interactions might have been more likely. Furthermore, we could not simply split the PBO group (comprised of 108 subjects) into 54 PBO and 54 A/R subjects because of low power. Using a simple test of proportions, a two group X^2 test with a 0.050 two-sided significance level would have 67% power to detect the difference between a Group 1 proportion of 0.600 and a Group 2 proportion of 0.400 (odds ratio of 0.444) when the sample sizes are 108 and 54, respectively (a total sample size of 162). To reach 80% power under these same assumptions, a total two-group sample size of 198 would be required, e.g., the sample sizes would have to be 108 and 90. In contrast to the 432 Ss in the original and revised designs, we would therefore start 530 Ss (106 in each of the 5 arms or 48/site + 2) in the unified design. As a result, Karen Wagner (UT Galveston) and Brian McConville (Cincinnati), our alternate sites, would need to become active sites, with Duke becoming the primary alternate site. The cost implications of initiating two additional sites and providing the necessary CC monitoring were considerable if not prohibitive.

Only a minority of sites favored a TADS A/R group, which echoed the opinions of various members of the CC and the SAB. In addition to the points made in the previous paragraph, their reasons reflected the inherent difficulty in defining how to operationalize the tradeoffs between two factors that determine the impact of treatment on outcome for the A/R condition: (1) access and (2) quality of care. As discussed below, we considered three A/R options: unfacilitated, HMO-standard care and facilitated care. The failure to agree on how best to structure the facilitated A/R option, which reflected the difficulty of establishing a crisp hypotheses for the A/R comparison, eventually resulted in rejection of this design option.

Assuming no access to mental health care, an unfacilitated A/R group in its simplest form would reduce to a no treatment comparison, i.e., this is an access driven option. The more likely outcome would mix limitations in type of care with financial barriers to access, so that the majority of those that sought care (most but not all subjects) would receive monotherapy consisting of brief supportive counseling or medication, probably with an SSRI. Site differences would be prominent in the mix of treatments available. While in some sense ecologically valid, there were two main objections to structuring the A/R group in this fashion. First, showing that more treatment is better than less treatment is not particularly interesting, since even without supporting evidence it is quite likely that within group change would have been for the better in all groups including A/R. Putting a floor under treatment received by the A/R group would render the comparison of greater policy relevance, assuming that study treatments are superior to A/R over the long term. Second and more importantly, TADS has an ethical responsibility to provide some level of support to families engaged with the study, which would not have been met other than by assessments in unfacilitated A/R.

In contrast, a quality driven option that eliminates access barriers entirely, HMO Standard Care (HMOSC), could have been constructed along the lines of a fixed dose study contrasting 5 doses of treatment: control (PBO), low (HMOSC), medium (FLX and CBT) and high (COMB). HMOSC would have been provided by the study team to insure that all subjects received the dose of treatment specified by the arm to which they were assigned. Many options were available to construct an HMOSC condition, but they all reduced to manipulating visit number, duration of treatment, and dose of medication. Since combination treatment is uncommon relative to monotherapy, a low dose COMB option would necessarily be excluded as lacking ecological validity. Conversely, because providing only one type treatment would disadvantage the comparison to either medication or CBT, another scenario might be to allow patients to choose between brief medication and psychotherapy. Given that medication is widely available, HMOSC would be a credible comparison condition to the study-delivered FLX and PBO conditions only if used at a low fixed (rather than flexible) dose for a short duration, say 20mg of FLX for 8 weeks. For psychotherapy, the mean number of mental health visits is 3-4, with a mode of 1, and CBT is much less common that supportive counseling; thus, 4 visits of supportive counseling over 6 weeks

might constitute a reasonable low dose psychosocial intervention. While superficially attractive, the HMOSC condition had two large disadvantages. First, no matter how we decided to construct the level of intervention, it would not match what is available at the point TADS reached the publication stage nor would it likely have satisfied critics, who would almost certainly say that HMOSC provided either too much or too little treatment, depending on the outcome and their policy preferences. Second, the unwillingness of patients/parents to discontinue treatments that seem to have been helpful, especially in partial responders, would present ethical and practical problems resulting in early termination unrelated to the efficacy of the treatments.

The preferred option, facilitated A/R, would have placed a "floor" under community treatment in order to bias the A/R group toward getting some treatment for the patient's major depressive disorder. In particular, we imagined that the facilitated A/R group might receive the following interventions: (1) psychoeducation regarding depression and the evidence in favor of specific types of treatment interventions, including a clear description of what types of treatment are provided by specific providers on the referral list; (2) encouragement and monitoring of treatment seeking; (3) minimal guidance regarding the types of treatment covered under the families' mental health benefit and/or options if the family has no health insurance; and (4) a small financial incentive that when coupled with the assessment reimbursement could be used to offset the cost of medication or psychological treatment interventions. Facilitated A/R would almost certainly have shown a larger effect size (a larger mean improvement and decreased variability in outcome) than unfacilitated A/R, which in turn would reduce the ability to find a difference between this condition and study-delivered treatments. However, the resulting contrast would be more interesting because a between group difference, if it in fact emerged, would better reflect quality of treatment and not simply barriers to access. Additionally, in facilitated A/R, the ethical obligations of TADS to the patient would be better met than in the unfacilitated A/R condition, which in turn would have made recruitment easier and lessened potential problems obtaining IRB approval. Nonetheless, without a consensual definition of the tradeoff between access and quality, the question to be answered by the A/R condition relative to study-delivered treatments was not crisp, which reduced the attractiveness of the A/R group considerably and ultimately led to rejection of this design option.

What age range defines an adolescent?

The RFP specifies an age range of 12-18, which roughly matches the developmental stage loosely termed "adolescence." However, because of the dramatic changes in the incidence of MDD across gender that occurs during the teenage years,[2,64] many investigators working in the area of depression have speculated on the influence of maturational factors and some have advocated for using Tanner Staging as an entry or blocking criteria for treatment studies in this area. Because the cost of tracking hormonal changes during puberty is prohibitive and the feasibility questionable, we elect to follow Tanner Stage as a baseline moderator of response to treatment as it seems to be a reasonable predictor of changes in incidence in any case.[65] We further elect to use an age range of 12-17 years old (12 to 17, inclusively) at randomization, which will allow 17 year old subjects to turn 18 during Stages II and III. To randomize 18 year old subjects would mean that a significant proportion of the sample might turn 19 years old during Stages III and IV, which in turn would impair the developmental integrity of the specific aims.

2.3. Sample Size and Power Estimates

Overview

The ***primary outcome measures*** rated by an Independent Evaluator (IE) will be as follows: (1) a composite/summary score on the Children's Depression Rating Scale-Revised (CDRS-R) and (2) a dichotomized CGI-Improvement (CGI-I) score (response, non-response) keyed to symptoms of major depression.

To insure compatibility with previous adult and pediatric studies, classification of patients as responders or non-responders with respect to the data analyses will be accomplished using the CGI-Improvement (CGI-I) scale, which will target DSM-IV major depression and its direct consequences (e.g. school

failure) only. Relative to baseline status, the CGI-I will be anchored as follows:. 1=very much improved, 2=much improved, 3= minimally improved, 4=no change 5=minimally worse, 6=much worse and 7=very much worse. Response on CGI-I will require a CGI-I of 1 or 2; partial response a 3; and nonresponse a 4 or worse.

Data analyses for both primary and secondary outcome measures will proceed in three steps. In step one, as recommended by Lavori (1994) [161], the initial analyses will be conducted under an "intent to treat" model in which all assessments points at all visits will be obtained and data analyzed irrespective of "dose of treatment." In step two, we will conduct analyses based on "observed cases available at each visit" (e.g., for 12 week analysis use only those patients who gave data at 12 weeks) that provide for the contributions of acceptability and tolerability to treatment efficacy, while at the same time protecting internal (and thereby external) validity through limiting threats to treatment integrity. In step three, we will conduct "completer analyses" using censored data from those children completing a full course of treatment. The characteristics of patients that are lost-to-follow-up will be compared with those that remain on study.

Once past intent-to-treat main outcome analyses as advocated by clinical trials experts[161, 162], subsequent analyses properly focus on moderator and, then, mediator effects to approach the question "which treatment for which teenager with what characteristics" that is of paramount interest to clinicians and to researchers attempting to refine treatments for larger effect sizes.[163, 164] In this regard, overall group differences in treatment outcome may be (a) moderated, wherein predefined subgroups (e.g., groups differing with respect to teenager comorbidity or to family characteristics) show differential response to assigned treatment modalities; or (b) mediated, whereby post-treatment factors may help to explain treatment effects (e.g., attendance at prescribed treatment sessions or change in cognitive variables may influence treatment response). Because we did not stratify on the basis of moderator variables and because the study was not "powered" to include detection of moderator or mediator effects, moderator and mediator analyses are secondary to the overall ITT analyses.

Wherever possible, analyses will be conducted using multilevel models (e.g. random regression in SAS, HLM, MLWin), which permit both analyses of univariate and multivariate continuous and categorical outcomes. Since TADS is an effectiveness study that is intentionally designed to answer a public health question, the fact that multilevel modeling allows statistically robust inferences from the sample population to the target population is a significant advantage. Alternatively, where appropriate, for example, because of a limited number of data points, analysis of covariance (for continuous variables such as CDRS-R) and logistic regression (for categorical variables such as response rate) will be used. As stratification/blocking variables, site and gender will be incorporated in all models. Given the intensive fidelity/reliability checks built into the protocol, site differences that move in the same direction--i.e., that differ in quantity or magnitude but not quality or direction of effect--can be seen as contributing to the generalizability of the findings. [162]

Specific analyses are as follows:

2.3.1 Primary Outcomes

a. Change in IE-administered CDRS-R total score across 12 and 36 weeks of treatment.

b. Response rate (i.e., proportion responding) on the IE-administered CGI-I at 12 and 36 weeks of treatment.

Primary Statistical Analyses

a. The primary statistical analyses will include all randomized subjects in the group to which they are initially assigned.

b. The principal treatment comparison will be between the combined treatment and monotherapy with CBT or FLX. Comparisons with PBO will be included to evaluate the validity of the trial during Stage I only.

2.3.2. Secondary Outcomes

a. Change in RADS total score over time

b. Changes in response rates for a diagnosis of MDD on the K-SADS-P over time

c. Change in non-MDD behavioral/symptomatic and functional outcome domains over time

d. Change in an unweighted composite score covering all domains of outcome over time

e. Change in clinician-rated Affective Disorders Screen (ADS, depression section), CGI-I, CGI-S and CGAS over time.

f. Change IE rated HONOSCA over time.

g. Number of Adverse events during the acute and maintenance phases

h. Long term maintenance of response to treatment for subjects who are responders at 12, 18 and 36 weeks and throughout Stage IV

i. "Time in response" (at 6 week intervals) in Stages I, II and III and (at 3 month intervals) in Stage IV.

Secondary Statistical Analyses

a. The primary outcomes will be analyzed separately for subjects who complete Stages I (acute study) and I-III (long-term study) in their assigned arms using the same random regression, analysis of covariance, and logistic models used for the primary statistical analyses.

b. In addition to the primary treatment comparisons accomplished on the primary outcomes for major, longitudinal data analyses using random regression models will be conducted on behavioral/symptomatic, functional and health economic variables.

c. Maintenance of response to treatment will be studied by the use of survival methods. Kaplan-Meier will be used in analyzing "time in response" over the 36 weeks of the randomized trial. Kaplan-Meier plots and log rank tests will be used for assessing differences in "survival" curves for two or more comparison groups in the absence of covariates. Overall differences in curves may be assessed as well as differences at specified time points during follow-up. When the effect of covariates are to be taken into account, Cox regression will be employed. Loss of randomization during the maintenance phase of the study will limit the value of treatment comparisons during Stage IV.

d. As suggested by Kraemer (personal communication), tests of interaction effects with treatment will be conducted to provide descriptive information on potential differences in treatment effectiveness due to moderating variables present at baseline (e.g., gender, severity of depression, and age) and time-varying mediating variables (e.g. compliance, changes in cognitions).

e. Descriptive statistics will be reported by treatment group for baseline characteristics, adverse events, attrition, and adherence to treatment.

f. Following the TADS publication policy, additional descriptive statistics and exploratory analyses will be conducted as proposed by the Steering Committee.

Sample Size and Power Estimates

Acute (Stage I) Outcomes: Detection of Differences in Response Rates

Stage I of the design, as outlined above, is a 12 week comparison of fluoxetine (FLX), cognitive-behavioral psychotherapy (CBT), combination (COMB) and pill placebo (PBO) in reducing major depressive disorder (MDD) symptoms and disability in adolescents. The primary endpoint for this phase is a marked improvement (a response) on the CGI-Improvement scale.

Consider the power for detecting differences in two or more (say, J) response groups based on the Pearson chi-square statistic, X^2. Under the null hypothesis, the sampling distribution of the statistic is an approximate central chi-square with J-1 degrees of freedom (χ^2_{J-1}). Under the alternative, the statistic is distributed as an approximate noncentral chi-square with J-1 degrees of freedom and noncentrality parameter $\lambda(\chi^2_{J-1,\lambda})$. Agresti[66] has given the noncentrality parameter for the Pearson statistic derived from a multinomial sample under general conditions. Thus, for a significance level α, the power $(1-\beta)$ to detect differences in J response (a dichotomous variable) groups given the alternative hypothesis is $P\left[X^2 > \chi^2_{J-1}(\alpha)\right]$ where $X^2 \sim \chi^2_{J-1,\lambda}$ and $\chi^2_{J-1}(\alpha)$ is the critical value.

Using the chi-square statistic, power estimates for detecting differences in response between the four groups were computed using the following assumptions:

1. H_0: $P_{(FLX)} = P_{(CBT)} = P_{(COMB)} = P_{(PBO)}$ where $P_{(FLX)}$ is the probability of response for FLX... and
2. H_A: $P_{(FLX)} = .60$, $P_{(CBT)} = .60$, $P_{(COMB)} = .80$, $P_{(PBO)} = .40$ (i.e., $P_{(COMB)}$ is .20 greater than $P_{(FLX)} = P_{(CBT)}$ and $P_{(FLX)} = P_{(CBT)}$ is .20 greater than $P_{(PBO)}$).
3. N = sample size in each treatment group = 108
4. No loss to follow-up (note a loss to follow-up might be classified as a nonresponse rather than an exclusion from analysis)
5. $\alpha = .05$ (two-sided test).

Under these assumptions the power can be shown to be greater than .99. Thus, the proposed study is well powered to detect overall differences between the four groups given the assumed alternative hypothesis H_A and a sample size of 108 per group.

In addition, after testing the four groups if comparisons of two treatment arms (e.g., $P_{(COMB)}$ versus $P_{(FLX)}$) are of interest, then if we assume

1. H_0: $P_{(FLX)} = P_{(COMB)}$ and

   H_A: $P_{(FLX)} = .60$, $P_{(COMB)} = .80$
2. N = 108 in each group
3. No loss to follow-up
4. p = .05 (two-sided test)

then the power is .89.

Furthermore, for a comparison of $P_{(FLX)}$ versus $P_{(PBO)}$ and the following assumptions

1. H_0: $P_{(FLX)} = P_{(PBO)}$ and

   H_A: $P_{(FLX)} = .60$, $P_{(PBO)} = .40$
2. and assumptions 2., 3., and 4. as above

then the power is .84.

Thus, the Stage I study is also adequately powered to detect a difference of .20 in response rates between two treatment arms.

Long-Term Outcomes: Detection of Differences in Response Rates

The full study involves a 36-week comparison of the three treatments FLX, CBT, and COMB, respectively. For this stage, the Stage I PBO group is no longer involved. Using the same Pearson chi-square statistic as in Stage I with J now equal to three groups and the following assumptions:

1. H_0: $P_{(FLX)} = P_{(CBT)} = P_{(COMB)}$ and

   H_A: $P_{(FLX)} = .65$, $P_{(CBT)} = .65$, $P_{(COMB)} = .83$

2. and assumptions 2, 3, and 4 as in Stage I

the power is .86.

In addition, if a comparison of the two treatment arms is desired (i.e., $P_{(FLX)}$ versus $P_{(COMB)}$ or $P_{(CBT)}$ versus $P_{(COMB)}$) then if we assume

1. H_0: $P_{(FLX)} = P_{(COMB)}$ and

   H_A: $P_{(FLX)} = .65$, $P_{(COMB)} = .83$

2. and assumptions 2, 3, and 4 as above then the power is .84.

Accordingly, we have adequate power with the estimated sample sizes to (a) detect a difference of .18 between $P_{(FLX)} = P_{(CBT)}$ and $P_{(COMB)}$ and (b) to detect a difference of .18 between the two groups $P_{(FLX)}$ and $P_{(COMB)}$ (i.e., $P_{(COMB)} - P_{(FLX)} = .18$ where $P_{(FLX)} = .65$).

Stage IV Follow-Up Detection of Differences in Response Rates

In Stage IV, randomization is lost as patients are followed openly. Since all analyses are exploratory, no power calculations are presented.

Other Considerations

With the exception that all tests are two-tailed in TADS, procedures to establish power for TADS are identical to those used to establish power for the Multimodal Treatment of Children with ADHD study (MTA: Helena Kraemer, PhD, statistical consultant).

As shown immediately above, TADS is powered to detect differences in treatment outcome assuming 108 subjects in each treatment group at each stage. This assumption is valid for the following reasons: (1) we assess all subjects at all assessment points irrespective of treatment status, (2) we include all subjects in the ITT analyses, and (3) we use multilevel models that are robust to missing data on the dependent measures. Specifically, TADS has been powered to detect differences in response rates on the CGI-Improvement score at 12 and 36 weeks assuming sample sizes of 108 in various treatment groups. At 12 weeks the study is designed to test response differences between 4 groups: fluoxetine (FLX) cognitive-behavioral psychotherapy (CBT), combination (COMB) and pill placebo (PBO). Furthermore, at 36 weeks and still assuming 108 subjects in each group we can still compare two treatment arms (e.g. P(FLX) versus P(COMB)) with greater than 80% power with assumed response rates (e.g. P(FLX) = .65, P(COMB) = .83) in each group. If treatment groups separate on the categorical "responder" analyses, for which adequate power is demonstrated, power should be greater to detect between-group differences on a continuous measure, such as the CDRS-R. Hence, we are confident that our power analyses indicate that we can detect meaningful clinical change for the primary outcomes at 12 and 36 weeks.

Outcomes other than IE rated MDD symptoms, while of crucial importance to the scientific goals of TADS as an effectiveness study, are secondary in an analytic sense. Therefore, absent guiding data in the scientific literature, no power analyses are presented for these analyses. However, assuming an equal impact on treatment outcome, power will likely be greater on theoretical grounds for continuous measures with excellent psychometric properties, such as the RADS, which ascertains MDD, as well as those, such as the Multidimensional Anxiety Scale for Children, which ascertain comorbid symptoms, than for categorical measures, such as a dichotomized CGI score. Hence the power analyses as presented serve as an appropriate if less well supported justification for power in secondary analyses.

Because sample sizes are smaller for completer analyses (e.g. an analysis at 12 or 36 weeks with only those subjects who have finished the entire protocol in their assigned treatment group), we do not have power over 80% to test differences between two treatment groups with the assumed response rate differences specified for the ITT analyses. To adequately power a completer analysis under the same assumptions would require a much larger sample size (e.g. 20 to 30% more patients) and the available funding for the trial is not adequate to accommodate this alternative. Nonetheless, completer analysis routinely yield significant between group differences because the effect sizes for more effective as contrasted to less effective treatments are relatively larger than in the ITT analyses as (1) the separation of the means (e.g., percent responders) is greater and (2) because standard deviations are reduced. It should also be noted, however, that randomization is no longer valid in completer analyses, making these analyses explicitly secondary.

Similarly, because the study is not powered to detect moderator (e.g. presence or absence of a previous episode of MDD) or mediator (e.g. compliance with treatment) effects, no power calculations are presented for these analyses. To power the study to detect moderator/mediator effects (represented as 3 and 4 way interactions) would require increasing the sample size well beyond what is practical in a study of this type. Nevertheless, most studies of this type identify meaningful moderator/mediator effects in part because of the increase power in power obtained in exploratory analyses from implementing less stringent controls on experiment-wise error.

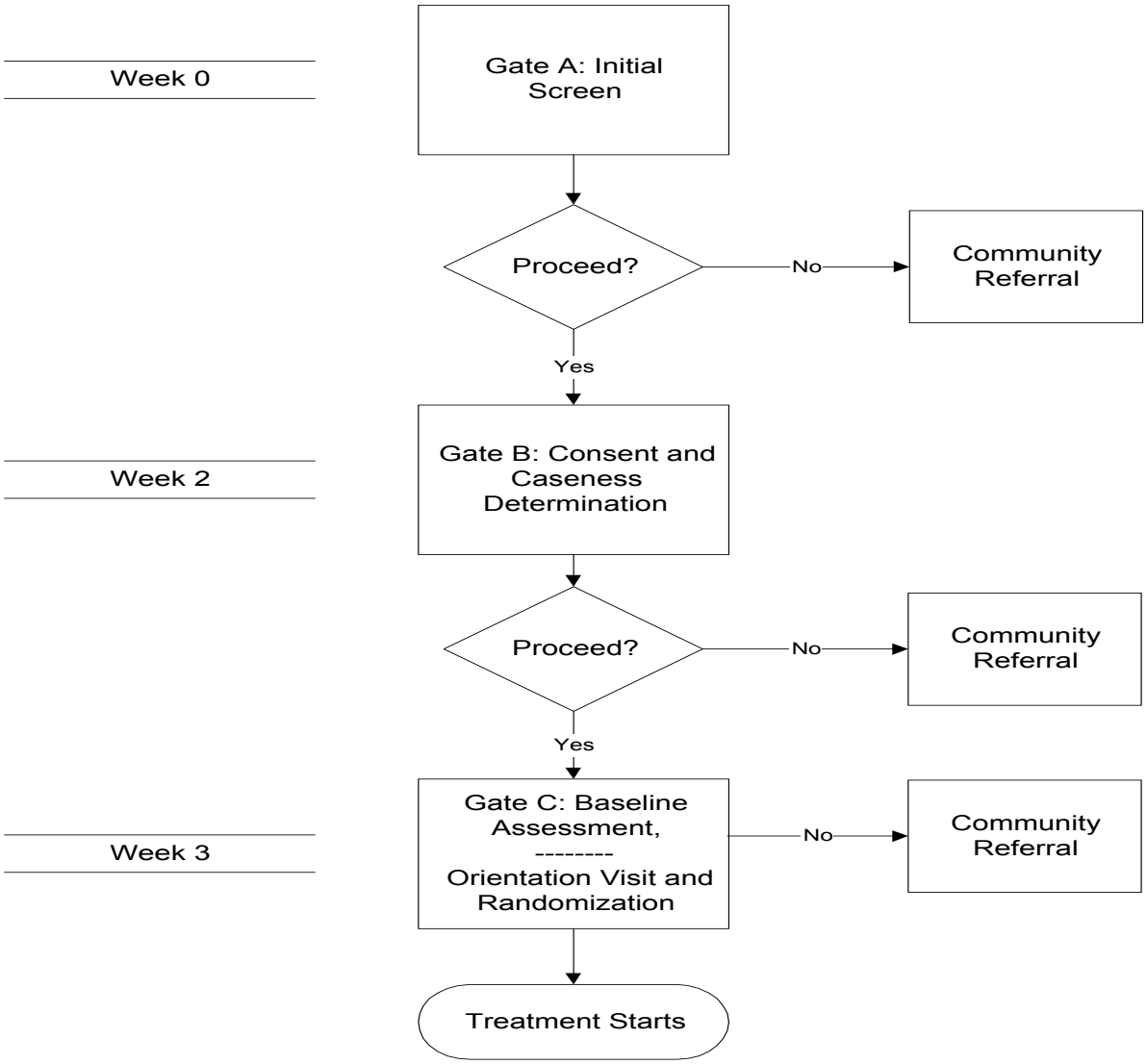
Diagnostics will be generated to check assumptions that are relevant to particular models and modification to the models will be made as necessary. These checks include tests for normality, homogeneity of variance, homogeneity of regression, and goodness of model fit. For example, if the data are nonnormal or the variance heterogeneous, appropriate transformations of the data will be made.

In addition to studying treatment response with time, the various statistical modeling approaches to repeated measurements will provide a vehicle for evaluating, comparing, and further educating the research audience concerning the relative merits of these alternative approaches to the analysis of clinical trials data. This may include methodological contributions with respect to Type I error and power considerations for hypothesis testing.

3. Subject Selection Procedures

There will be a minimum of 432 subjects who enter the treatment study, 48 at each of nine sites, evenly divided at baseline among the four treatment groups. There will be no attempt to obtain samples at each site that are representative of the population as a whole in terms of gender, SES, or ethnicity, i.e., other than stratifying by site, no stratification strategy is proposed. However, due to the broad range of recruitment and referral sources and the inherent diversity of the sites, the study sample as a whole will be broadly representative of the population who suffer with this disorder.

Figure 2: TADS Entry Procedures



3.1. Inclusion and Exclusion

The most important inclusion and exclusion criteria and their rationales are summarized in Tables 2 and 3 and discussed in detail in Section 3.3:

Table 2: Inclusion Criteria and Rationale

Inclusion Criterion	Rationale
Primary Diagnosis DSM-IV of MDD Pervasive and stable	Disorder of interest Matches justification for treatment and minimized "PBO" response
CDRS-R at Gate C ≥ 45	Indicates clinically significant MDD on primary outcome measure
Ages 12-17 years inclusive	Matches developmental correlates of treatments and outcome domains
Grade 6 to 12	Matches developmental correlates of treatments and outcome domains
Full-Scale IQ ≥80	Lower IQ may not permit specified CBT treatment
Medication-free before start of study	Carry-over effects confound study treatments
Outpatient	Inpatient care or incarceration confound study treatments

Table 3: Exclusion Criteria and Rationale

Exclusion Criterion	Rationale
Bipolar disorder	May require additional or different treatments
Severe Conduct Disorder	May require additional or different treatments
Substance Use/Abuse/Dependence	May require additional or different treatments and/or risk of interaction with medication
Pervasive Developmental Disorder(s)	May require additional or different treatments
Thought Disorder	May require additional or different treatments
Suicidality or homicidality	Unethical to randomize to PBO
Concurrent treatment with psychotropic drug (stable stimulant for ADHD permitted) or psychotherapy outside study	Confounds internal validity of treatment assignment
Two previous failed SSRI trials or a failed trial of CBT for depression	Not likely to respond to study treatments; may require additional treatments
Intolerance to fluoxetine	May require non-study drug treatment; risk of side effects
Non-English speaking patient	Cannot complete study assessments
Pregnancy or breastfeeding	Potential risk of medication to fetus
No phone in home	Inability to monitor treatment; feasibility

3.2. Patient Screening

As illustrated in **Figure 2**, subjects enter TADS through a three-gate entry procedure designed to ensure that patients evidence stable, pervasive major depression at the start of treatment. Patients will be selected without regard to race, gender, or ethnicity.

Patients will be recruited from five sources: (1) site clinics; (2) schools and juvenile justice facilities; (3) primary care physicians; (4) other mental health providers; and (5) paid and public service advertisements in local media, including newspapers, radio, and TV. Each site will follow a uniform set of rules on how to recruit subjects.

The expected average time from Gate A to randomization will be 2-3 weeks, with a range of 2 (minimum) to 6 (maximum) weeks.

- **Entry Gate A**. Gate A (or the first "gate") is a semi-scripted telephone or face-to-face screening procedure to elicit preliminary inclusion/exclusion information and to provide additional information to the caller, including the need for further assessment.
- **Entry Gate B.** Gate B involves determination of "caseness" (intake procedure, diagnostic assessment, and formal presentation of the informed consent agreement). At the end of Gate B, if the prospective patient continues to meet all eligibility criteria, then he/she may be ELIGIBLE for randomization to treatment.
- **Entry Gate C**1. The Gate C1 Baseline Assessment (C1) consists of ratings and assessments for the parent about the parent, about the teenager, and about the family and parent/teenager interactions; and for the teenager about the teenager, family, and parent/teenager interactions.
- **Gate C2.** The Gate C2 orientation will confirm consent and assent, inform the family of their treatment assignment, introduce them to other treatment team members and will review procedures for managing suicidality and maintaining confidentiality

3.3. Inclusion and Exclusion Criteria by Gate and Informant

Patients and families must meet the following inclusion AND exclusion criteria defined by study gate and informant:

Inclusion Criteria

- **Gender (Gate A):** Both males and females will be admitted to the study.
- **Age (Gate A):** Subject must be 12 to 17 years old, inclusively (i.e., must be at least 12 years old and NOT yet 18 years old) at the point of consent.
- **Grade in School (Gate A):** Subject must be at least in the sixth and at most in the twelfth grade at the point of consent.
- **Diagnosis (Gates B and C1):** Subjects must meet DSM-IV criteria for a primary diagnosis of MDD on the K-SADS-P at Gate B and again at Gate C.
- **CDRS-R:** Subjects must exhibit an IE-rated CDRS-R summary score $\geq$ 45 at Gate C1 (baseline).
- **Stability and Pervasiveness:** On clinical interview including information from both patient and parent, subjects must exhibit stable dysphoria defined as item 1 (depressed mood) and/or 2 (anhedonia) and pervasiveness (defined as present most of the time in at least two of three contexts: at home, at school or with friends) for at least six weeks prior to consent at Gate B.
- **Family Members (Gate A):** Subjects will have continuously resided with a primary caretaker (defined as a parent(s), close relative functioning in loco parentis, legal guardian, or foster parent) who has known the teenager well for at least 6 months before study entry and is legally able to sign the consent form.
- **Informed Consent and Compliance (Gate B, C1 and C2):** After considering all aspects of study participation as presented during the study entry procedures (see Gate B description), subjects and families must agree in writing, to "full participation" in the study. **Full participation is further defined as agreement to comply with the requirements of each of the treatment groups and of all assessment procedures irrespective of treatment assignment or status.** Random assignment to treatment will not occur until after such agreement. At the Gate C2 orientation visit, families will be asked to review all the requirements for each component of the study (treatment and assessment) just before being told their group assignment.

Exclusion Criteria

Patient Reasons for Exclusion:

- Teenager is currently or has previously been a participant in another MDD treatment study. (Gates A, B, C1, C2)
- Teenager is currently or within the preceding 3 months has been a participant in another clinically referred MDD assessment study. School screening or other population study resulting in clinical referral is not an exclusion. (Gates A and B)
- Teenager scores below 80 on Full Scale IQ, initially estimated from the two-subtest WISC-III screening procedure (vocabulary and block design), and if needed, when confirmed on the full WISC-III (Gate B). **If a potential patient has had a verified (e.g. reviewing the report indicates valid data with acceptable FSIQ score) WISC in the three years previous to TADS enrollment, the WISC does not need to be readministered.**
- Teenager is pregnant as indicated by history or a positive pregnancy test drawn at Gate B. Sexually active girls must consent to using an effective form of birth control, either hormonal (BCP, Depo-Provera or Norplant), spermicide (foam or vaginal suppository) or a barrier method (condoms, diaphragm, cervical cap) or a combination of barrier/spermicide contraception in order to participate in the study.
- Teenager is breastfeeding and unwilling to stop.
- Teenager meets current or past DSM-IV criteria for bipolar affective disorder (BPAD) (Gate B and C1). Note: Depending on how the interviewer applies the DSM-IV criteria set for BPAD, the likelihood of diagnosing BPAD can vary considerably across clinicians. It is important that normative, conduct- or depression-related affective dysregulation, which might under some interpretations qualify a potential subject for a diagnosis of BPAD, Mixed, should not deprive a teenager of the benefits of being in the study unless the diagnosis of bipolar disorder is unequivocal. Doubtful cases should be referred to the cross-site Caseness Panel.
- Teenager meets DSM-IV criteria for Obsessive Compulsive Disorder (OCD) severe enough to require specific treatment for OCD, e.g. SSRI and or CBT. (Gate B)
- Teenager meets current DSM-IV diagnostic criteria for current Conduct Disorder (CD) on the K-SADS-PL **and** (1) conduct symptoms are deemed not to be secondary to MDD **or** (2) patient is deemed unlikely to comply with study assessment and treatment procedures. All such patients must be referred to Caseness Panel for discussion. (Gate B).
- Teenager has been hospitalized for any psychiatric indication in the three months preceding consent. Hospitalization is defined as: inpatient unit, partial hospitalization unit or residential treatment facility. Being on probation or residing in a group home or foster care placement does not constitute a sufficient reason for exclusion if in the opinion of the site team the teenager would be a suitable candidate for TADS treatment.
- Teenager is confined to jail or to a juvenile justice facility. If a teenager is court-ordered to treatment, that subject may be included if in the opinion of the site team he/she is a suitable candidate for TADS treatment (Gates A and B)
- Teenager meets DSM-IV criteria for opiate or hallucinogen use (e.g., LSD, ecstasy, mescaline, peyote, PCP) and does not agree to cease using opiates and/or hallucinogens for the duration of the study. (Gate B)
- Teenager meets DSM-IV criteria for a primary or co-primary substance abuse or dependence disorder other than nicotine dependence. (Gate B)
- Teenager meets DSM-IV criteria for autism, PDD or Asperger's syndrome. (Gate B)
- Teenager has been diagnosed as having a current or past psychotic disorder, including schizophrenia-spectrum disorders, psychotic major depression or an organic psychotic disorder.

Doubtful cases, such as transient auditory hallucinosis, should be referred to Caseness Panel. (Gate B)

- Teenager is currently receiving a neuroleptic drug or has required chronic (greater than 2 weeks) of neuroleptic treatment in the 6 months before study entry (defined as the Orientation Visit). Inappropriate neuroleptic treatment, for example, brief treatment with risperidone for anxiety, does not meet this exclusion requirement. (Gate A)
- Teenager has a major neurological disorder, such as cerebral palsy, epilepsy, post-head injury syndrome or post infectious neurological disorder, which requires ongoing treatment with a prohibited (see Appendix A) medication or that would interfere with his/her full participation in the study. (Gate B)
- Teenager has a major medical illness that requires a prohibited episodic or chronic systemic medication (see Appendix A) or that would interfere with participation in the study (e.g., frequent hospitalizations, frequent school absences). (Gates A, B)
- Teenager has failed a previous trial of fluoxetine judged adequate in dose (20 mg) and duration (6 weeks) or teenager has a history of intolerance to FLX. (Gates A, B)
- Teenager has failed two previous SSRI trials judged adequate in dose (20 mg of citalopram or paroxetine, 50 mg of sertraline or 100 mg of fluvoxamine) and duration (6 weeks).
- Teenager is taking psychotropic drug that is on the episodic or chronic prohibited list. (Gate A).
- Stable treatment with a psychostimulant (Adderall or IR or sustained methylphenidate or Dexedrine; pemoline and methamphetamine are excluded) for ADHD is acceptable under the following conditions. First, stable means that total daily dose has not changed by more than 25% during the 12 months preceding study Gate B consent. Second, written agreement is obtained from the patient's prescribing physician **between Gates B and C** to collaborate with TADS procedures for managing psychostimulants during TADS. For subjects in pills conditions, this means ceding control of stimulant treatment to the study pharmacotherapist.

  In the CBT alone condition, the prescribing physician continues to monitor psychostimulant treatment within three parameters: (1) change in psychostimulant type of greater than 25% total daily dose is not permissible without prior consultation with the CBT therapist; (2) treatment with other psychotropic medications or recommendations regarding the need for additional or changes in psychotropic medication is not permissible; and (3), additional psychosocial treatment or recommendations regarding changes in psychosocial treatments is permissible.

  Note: If additional treatment for ADHD outside the TADS protocol becomes necessary on an urgent or emergent basis, such treatment will be provided as required under ASAP provisions and, if needed, by referral to community care. (Gates A and B)
- Teenager has failed a previous trial of CBT for depression within the previous 2 years judged adequate by at least 12 treatment sessions over a period of less than 1 year conducted by a cognitive-behaviorally oriented licensed mental health provider.
- Teenager poses a significant risk for dangerousness to self that makes participating in a randomized controlled trial that includes a PBO condition inadvisable. First, all subjects who have been hospitalized in a psychiatric or medical (e.g. ICU) unit because of a suicide attempt (irrespective of psychiatric diagnosis) within 3 months of Gate B will be automatically excluded until this criteria is no longer met. Second, excessively "high risk" cases will be excluded if in the opinion of the site team and the TADS Caseness panel, participation in TADS poses an unacceptable risk. High risk is defined as follows: (1) a suicide attempt or other significant act involving intentional self-harm, e.g. cutting or overdose, resulting in medical attention (e.g. hospitalization or visit to ER or emergent referral to mental health clinic) within 6 months of Gate B; (2) repeated suicidal or homicidal ideation with clear intent or plan within six weeks of Gate B; or (3), based on a large literature

implicating family discord in completed suicide,[87] as current suicidal ideation without intent or plan **and** grossly inadequate family supervision/functioning.

- Using the same decision rules as established for dangerous to self, teenager poses an unacceptable risk for dangerousness to others, as indicated by (1) homicidal (or other violent) ideation, intent, plan or action; (2) use of illegal weapons; or (3) the presence of potentially lethal activities, such as extremely reckless driving or unsafe use of legal firearms or other weapons.
- Teenager is non-English speaking defined as the inability to complete study measures, IE ratings or to participate in treatment without the assistance of a dedicated translator or translation of study measures. So as not to exclude partially bilingual children who otherwise might be good candidates for TADS treatment, assistance from bilingual study staff is permitted.
- Teenager is a victim of ongoing or previously undisclosed child abuse requiring new DSS report or active DSS supervision. Doubtful cases should be referred to Caseness Panel. (Gates B)
- Teenager, for any reason, has missed more than 25% of school days in the 2 months preceding randomization. Home schooling does not require exclusion from the study under this exclusion criterion. Doubtful cases should be referred to Caseness Panel. (Gates A, B).
- Teenager does not agree to dangerousness and confidentiality procedures specified at Gate C2.

Parent Reasons for Exclusion:

- Non-English speaking primary parent or caretaker defined as the inability to complete study measures, IE ratings or to participate in treatment without the assistance of a dedicated translator or translation of study measures. So as not to exclude English-speaking subjects whom otherwise would be good candidates for TADS treatment, assistance for partially bilingual parents from bilingual study staff is permitted. (Gates A, B, C1)
- Parent does not agree to dangerousness and confidentiality procedures specified at Gate C2.

Household Reasons for Exclusion:

- Subject residing in a home without telephone service. (Gates A,B)
- To avoid cross-contamination between treatment conditions and non-independence of observations, only one teenager per family may participate in TADS. When two or more children are eligible, illness severity (higher severity is preferred) and patient/parent preference should be weighted in that order when selecting the sibling for TADS.

Caseness Panel Mechanism

To make sure that study eligible subjects are not excluded and to guarantee cross-site uniformity by establishing a series of common precedents, we will use a Caseness Panel mechanism to review exclusions that call for clinical judgment. Specifically, sites will ask Caseness Panel to review a subject that a site wants to include in TADS but for whom (in the opinion of the site team) study eligibility is open to question. Caseness Panel will meet at the beginning of each biweekly PI conference calls. Between calls, decisions regarding study entry that must be made prior to the next scheduled call can be made in consultation with one of the CC Executive Committee clinicians (Drs. March, Curry or Wells). It is expected that a site will seek Caseness Panel review for subjects falling under the exclusion rules defined below for whom uncertainty exists regarding suitability for participation in TADS:

- MDD complicated by possible co-primary CD symptoms.
- Possible bipolar disorder, especially mixed states.
- Substance use versus abuse/dependence.
- Legal entanglements, such as parole or DSS involvement.

- Medical exclusions.
- "High risk" suicidality or homicidality.
- School attendance.
- Language exclusion.
- IQ exclusion (<80 but >70) in which cultural or psychiatric factors (e.g. test anxiety) are present suggesting that the teenager would be capable of completing TADS treatment **and** assessment procedures.
- Disagreement between clinician (Gate B) and K-SADS (Gates B and C) diagnosis of MDD.

Commentary on exclusions for comorbidity with BPAD, conduct disorder or substance abuse

Epidemiological data suggest that the incidence of MDD, BPAD, CD and substance abuse/dependence all rise dramatically in adolescence often in the same patients.[68] Depressed subjects showing complex comorbidity are much more likely to require intensive services, including inpatient care, in part because of a higher probability of dangerousness.[69, 70] Hence, it is critical that the experimental design include in/exclusion variables formulated to maximize generalizability of the study results to the target population while at the same time restricting threats to the internal validity of the study, particularly via subject attrition and noncompliance with assessment and treatment. It is equally important that the study conform to the highest ethical standards, which require that treatments be appropriate to the study sample. Because comorbidity with BPAD, CD and substance use are especially critical (and clinically problematic) we justify our design choices for in/exclusion criteria for these potential comorbidity below.

As pointed out earlier, there is substantial overlap between MDD and BPAD, especially in adolescents. Though not without controversy,[71] it is likely that the treatment of bipolar depressed adolescents with an SSRI presents an increased risk for the induction of mania.[72, 73] Besides lying outside the scope of the RFP, which targets MDD, including bipolar patients therefore would require treatments (for example, mood stabilizers and family case management[38]) not allowed by the protocol rendering their inclusion unethical and impractical.[74] Consequently, we feel on solid ground excluding potential subjects with a past or current history of BPAD.

A much more difficult design choice is presented by data showing that the risk for BPAD in adolescence is increased by the presence of pre-pubertal MDD or a positive family history of BPAD.[75] Preliminary data suggests that the risk of conversion to BPAD with medication treatment is largely confined to patients with a positive family history of BPAD.[75] If the studies of CBT[17] and fluoxetine[56] that excluded BPAD are reliable guides, the incidence of new onset mania is likely to be very low. Therefore, excluding subjects with either pre-pubertal MDD or a positive family history of BPAD would unreasonably reduce generalizability of the study results and would unacceptably slow sample recruitment. Including subjects with both pre-pubertal MDD and a positive family history of BPAD could conceivably present a somewhat greater risk to the individual teenager and, if conversion to mania with medication management caused significant subject attrition, to the internal validity of the treatment comparison vis-à-vis MDD as well. Nevertheless, since the absolute magnitude of the risk for conversion to BPAD in this group is unknown and likely to be small, we elect not to exclude these subjects but to monitor carefully for development of hypomania or mania.

This study requires a primary diagnosis of MDD, which in turn decreases the probability that patients with severe CD will enter the study. However, many depressed adolescents exhibit conspicuously disruptive behaviors and, in fact, referral to a clinic for treatment is almost certainly enhanced (via Berkson's bias) by the presence of comorbidity of all sorts, including oppositional-defiant and conduct disorder.[76] Excluding patients exhibiting disruptive behaviors therefore would seriously weaken the external validity of the study and would present a serious problem with respect to recruitment. As importantly, in a treatment study like this one, disruptive behaviors associated with MDD are quite

likely to improve in patients responding to treatment and constitute an important domain of outcome beyond the pure DSM-IV depression cluster.[19] On the other side of the argument, two factors mitigate against accepting severely conduct disordered patients into a trial such as the one proposed here. First, compliance with assessment and treatment may be adversely affected by CD, although the entry gates, which are primarily geared toward recruiting subjects with stable dysphoria, will tend to bias the sample toward higher compliance with the study protocol. Second and more importantly, while we do address family factors identified as important in angry oppositional depressed youth,[77,78] our treatments do not include the kinds of family and case management interventions required for the severely conduct disordered patient.[79] To achieve a reasonable balance between these competing imperatives, we have elected not to exclude subjects based on a diagnosis of ODD or CD, but rather to exclude potential subjects with comorbid CD whose (1) conduct symptoms are not secondary to MDD and (2) who are unlikely to be able or willing to comply with study assessment and treatment procedures.

While substance use will not be a cause for exclusion from the study, comorbid substance abuse is a third complicating factor when mounting a treatment study of depressed adolescents, many of whom will have had some involvement in illegal substances.[80, 81] As with BPAD or CD, depressed adolescents with a primary diagnosis of substance dependence require specific treatment for substance abuse/dependence,[82,83] making their exclusion easy. In many cases, these excluded youth will also be those manifesting severe CD and/or BPAD.[84] Unfortunately, the boundary between substance abuse and normative substance use is much less clear, depending primarily on the interviewers interpretation of functional impairment associated with the intake of substances.[85, 86] Excluding youth who use/abuse substances would unduly threaten generalizability and subject recruitment. In this regard, we elect the following decision rule/procedure. With three exceptions, adolescents referred to the study with substance dependence or a primary diagnosis of substance abuse will be excluded.

Because many depressed adolescents use tobacco products, which by themselves will not interfere with TADS treatments, it would seem unreasonable to make nicotine use, abuse or dependence an exclusion as doing so would dramatically reduce sample representativeness. Conversely, because opiates are subject to pharmacokinetic interactions with FLX (specifically, FLX inhibits p450 isoenzyme 2D6 that metabolizes opiates) that could promote opiate intoxication, illicit opiate use during but not prior to the study is an exclusion. (Dextromethorphan in cough and cold preparations taken for their intended purpose according to the directions is not an exclusion; dextromethorphan taken for illicit purposes, e.g. to get “high,” is an exclusion.) Thus, a teenager wanting to participate in TADS must be willing to cease opiate use to participate in TADS. Similarly, hallucinogens (e.g., LSD, ecstasy, mescaline, peyote, PCP) are subject to adverse pharmacodynamic interactions with FLX (increase risk of adverse reactions) making hallucinogen prior to TADS coupled with lack of agreement to stop hallucinogen use an exclusion criteria. If opiate or hallucinogen use is discovered during TADS, such use always should be discouraged by the treating clinician irrespective of treatment assignment, and, if necessary, should be managed under ASAP procedures.

Commentary on Exclusion for Dangerousness

A panoply of clinical and epidemiological studies have documented the relationship between suicide attempts and completed suicide and MDD.[70, 80] Because suicidality is an intrinsic part of the spectrum of depressive symptoms, it isn’t possible or reasonable to exclude potential subjects simply on the basis of having suicidal ideation. Conversely, in a randomized controlled trial, where one of the treatment conditions, PBO, is "inactive," it would be ethically indefensible to enroll a patient at high risk for suicide in the trial[74] even though active treatment has a high probability of reducing suicidality.[17] TADS will exclude any potential subject who has recently been hospitalized because of a suicide attempt. In addition, we consider for exclusion "high risk cases" using the Caseness Panel mechanism as noted above. Although much less is known about homicidal ideation in adolescent MDD, homicidal and suicidal ideation are clearly associated with completed suicides among teenagers.[69] Hence, we elect to use the same exclusion rules for "dangerousness to others" as we do for "dangerousness to self." These recommendations are in accordance with the Practice Parameters on Suicide (Cynthia Pfeffer and David

Schaffer, Eds.) put forth by the American Academy of Teenager and Adolescent Psychiatry, which will be included in the TADS inservice manual.

Commentary on Confidentiality

In general, what the teenager says during assessment or treatment sessions is confidential. The exceptions are in cases of suicidality, homicidality, child abuse (sexual or physical), or need for medical care.

All TADs subjects will be required to agree to a no-suicide contract at the time of gate C2 interview. This includes an agreement to inform the therapist and the parents of suicidal thoughts or impulses, and to take other steps as may be outlined for individual adolescents in the contract, which are designed to minimize the risk of escalation in suicidal status. Cases in which the adolescent does not respond positively to these procedures will be handled through ASAP, and in the case of suicidality, the TADS Suicidality Procedures Manual.

Adolescents and parents will be informed of the other conditions that necessitate breaking confidentiality during the C2 interview, and if they do not agree to these, they will not be randomized to treatment. Cases of homicidality require notification of the intended victim and the police. Cases of abuse must be reported to the local department of social services (or equivalent name). Cases in need of medical care will be reported to the parents so that care can be provided.

Two other types of problems may necessitate breaking of confidentiality: disclosure of pregnancy during treatment; and disclosure of substance abuse during treatment

Pregnancy is an exclusion for TADS. New pregnancy will be tracked during TADS via teen/parent disclosure and by monitoring menstrual cycles. A missed MP in an otherwise regular teen will prompt the primary therapist to ask about pregnancy. With the caveat that state law and site IRB procedures take precedence, a positive disclosure will prompt informing the responsible parent. Pregnancy by itself does not require premature termination, but must be handled through ASAP procedures to determine what is in the best interests of the patient/family.

Substance dependence, except for nicotine, is exclusionary for TADS. Use of hallucinogenics or of opiates is also exclusionary. Other drug use during TADs will be reported to parents if in the judgment of the therapist and site treatment team, the use rises to a level of dangerousness. Otherwise, adolescents will be encouraged to disclose (non-dangerous) use to their parents in the interest of effective treatment and openness within family communication.

3.4. Study Entry Procedures

The recruitment/sampling strategy is designed to enter into treatment a volunteer clinical sample that matches clinical patients seen in general clinical practice. As noted earlier, each site will enroll 48 patients (2/month), age 12-17 inclusive, using a multiple gating procedure in which patients will be screened (Gate A), consented (Gate B), assessed for study eligibility (Gates B and C1), and if eligible, randomized (Orientation visit) to one of the four treatment groups. Patients will be selected without regard to race, gender, or ethnicity. Each site will follow a uniform set of rules on how to recruit subjects, and as stated above, will take consecutive referrals arising from these efforts. To aid uniformity across the nine sites, a standardized "recruitment package" for presenting the study to the referral sources and a standardized "entry/consent package" for presenting the study to subjects and families will be used.

3.4.1. Sample Sources and Recruitment Procedures

Children and adolescents of both sexes ages 12-17 inclusive with a DSM-IV diagnosis of MDD comprise the target population to which the study results are intended to generalize. To minimize site-specific selection biases on variables such as sex, age or referral source, and to maximize representativeness, subjects will be entered into the study *consecutively* at all sites. All potential patients within reasonable driving distance of each site comprise the sampling frame or accessible

population for selection to treatment. Those children and adolescents actually entered into the intervention comprise the study population. To ensure that the selected study population will generalize back to the target population, the sampling/recruitment procedures outlined below define how the sample is drawn from the accessible population, paying careful attention to procedural uniformity across sites.

Subjects will be referred for entry into the study from multiple sources, including:

- Mental health identified children, i.e., children already coming to a clinic (including self-referrals to a mental health clinic);
- Primary care identified children (pediatric and family physicians);
- Teacher or school identified children (i.e., school refers through the parents or primary caretaker);
- Families who self-refer as a result of advertising (newspaper, radio, word-of-mouth).

The relative percentage of subjects coming from each of these referral sources may vary across sites due to differences in school systems, primary care networks and in response to other community norms, including issues of ethnicity and culture. It may not always be possible to determine precisely the family's entry into the study (since they may hear about it through multiple sources), but information will be obtained from the families to determine their particular source of information and route of entry into the study. While the source(s) of the referral will be recorded, there will be no attempt to stratify the sample based on referral source or to obtain a minimum proportion of any of the referral sources. Each site will attempt to recruit from the full-range of sources, not just one "convenient" source.

3.4.2. Initiation of recruitment

Recruitment will involve (1) mailing written information about the study to mental health practitioners, school personnel, and primary care physicians; (2) contacting suitable referral sources about presentations; and (3) advertising the study through press releases, contacting advocacy groups, and, where possible, newspaper, TV, and/or radio public service announcements.

The "recruitment package" will consist of: (1) written materials in the form of general flyers and pamphlets describing the study; (2) general guidelines for site personnel to use in describing the study over the telephone to potential referral sources; and (3) scripted advertisements. The "entry/consent package" is implemented when families contact the site based on one or more of the referral sources described above. In addition to specific written materials, the "entry/consent package" consists of a uniform series of steps or "gates" that must be followed in order for a subject to be considered qualified to enter the study. The expected time from Gate A to randomization will be 3 weeks, with a range of 2 (minimum) to 6 (maximum) weeks.

3.4.3. Screening Gates

(1) Gate A (or the first "gate") is a semi-scripted telephone or in-person screening procedure that elicits preliminary inclusion/exclusion information and provides information to the caller, including the need for additional assessment procedures. This screening phase is intended as a first-contact point and will decide only clearly excluded cases (e.g., age, grade in school, already on anti-depressive medication). All others will go on to Gate B (if they agree to do so). If the initial screen results in preliminary qualification (agreement by the caller to be considered further is part of that qualification), then Gate B is entered as soon as possible after the screening. If the preliminary elicitation of information disqualifies the subject from further consideration (e.g., if teenager is too young), or if they do not agree to go on to Gate B, a list of referring organizations or possible treatment settings can be provided on request, including the site clinic and other available site or community specific services. At this point, subjects remain under the care of the pre-study clinician (or no clinician, if none was present before initiating study entry procedures). Any Gate A applicants who call in a crisis will be clinically referred and invited to call back when they are ready.

Specification of the Referral List

For patients referred to clinical care at any point during the study, each site will maintain a standardized referral list consisting of two or three examples of practitioners or practice groups that conform to acceptable community standard care for adolescents with MDD or other psychiatric disorders. Each list will include at least two and not more than four from the following:

- Child and adolescent psychiatrists
- Child and adolescent psychologists
- Pediatrician and/or family physicians
- Social workers

While mental health or primary care practitioners at the TADS site may not for ethical reasons be excluded from the list of mental health providers, TADS team members may not participate in the care of TADS patients outside the boundaries of TADS itself.

If Teenager is Taking Medication at Gate A

Children who are taking tricyclic antidepressants, any SSRI, buspirone or other anxiolytic, other antidepressant (e.g. bupropion, nefazodone, venlafaxine or mirtazepine) or mood stabilizer (e.g. lithium, gabapentin, valproate, topiramax, lamotrigine, or carbamazepine) at Gate A are not eligible for the study and cannot be scheduled for the Gate B visit. Family and patient are informed that the study is for children who are depressed and have not taken any medications for depression (prescription or non-prescription) for 2 weeks or longer. (Note that nonresponse to FLX eliminates those who currently meet MDD criteria and are taking FLX; responders to FLX would be ineligible because they would not meet MDD criteria. All others follow the in/exclusion rules outlined above.) If the teenager/family wishes to consider discontinuing current medication, the teenager/family should consult with their private treatment provider and make their own informed decision. A decision to discontinue treatment is between the teenager/family and the treating physician and is not to be made or influenced (pro or con) by TADS staff. To assist the teenager/family and the treating physician in making an informed decision about whether to participate in TADS, the study team will provide, at the request of the teenager/family, a description of the study (parent and physician standard recruitment materials) as well as a cover letter addressed to the parent that provides a brief explanation of the rationale for stopping medication before Gate B can be scheduled. If it is agreed between the teenager/parent and their physician that medication should and can be safely discontinued under the care of their physician, the letter will state that the parent should contact the TADS site team to schedule a Gate B visit two weeks after the last dose of medication has been taken.

(2) Gate B follows as soon after completion of Gate A as possible. The purpose of Gate B, which is standardized across all sites, is to ascertain "caseness" and to establish informed consent. The Gate B visit includes a thorough overview of the study in the form of written materials, including the consent/assent forms, and a face-to-face meeting with study personnel. Each of the four treatment arms will be clearly described, including equal probability of assignment to one of the four groups.

If Gate A eligibility criteria are met, a Gate B appointment can be made as part of the Gate A phone screen. Once an appointment is set, the parent(s) or primary caretaker(s) is (are) reminded via an appointment letter and telephone call to come to the site's clinic for an in-person visit that includes both the teenager and the primary caretaker(s). If possible, both parents are expected to attend. Included with the appointment letter are written materials describing all four treatment arms of the study in greater detail.

Note that Gate B is divided into B1 and B2 to reduce subject and investigator burden by distributing assessments across 2 days. Per site option, the B Gate assessments can be completed on one day. It includes an intake procedure consisting of formal presentation of the informed consent form and assent agreements as well as a clinical interview of the teenager and parent, an IQ test, the basic reading subtest of the WIAT Screener and a diagnostic assessment with the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime versions (K-SADS-PL). Parenthetically,

subsequent administrations involve just the present state version (K-SADS-P) or just the affective disorders module from the K-SADS-P, the K-SADS-AD.

Before obtaining consent and assent, a temporary clinician (masters or doctoral level) case manager is assigned to the subject (if the subject continues, this case manager assignment will stay in effect at least until the Orientation Visit).

Specific Gate B procedures are as follows:

It is preferable that the site PI or, if necessary, Co-I conduct the consent procedure, after which the remainder of the Gate B procedures may be turned over to site staff as appropriate.

After carefully presenting the study and answering any questions that families may have, the consent form is presented to the parent(s), with the caveat that agreement by the subject and family does not guarantee entry to the study since diagnostic and other qualifying assessments have not yet been done. Subjects must sign an assent form or co-sign the consent form as specified by the site IRB.

Procedures for managing dangerousness and confidentiality will be introduced as part of the informed consent procedure and reinforced at Gate C2.

If teenager/family refuse further participation, then the standardized written referral information will be provided at the parent's request.

If teenager/family consent to continue, the teenager is administered a 2 sub-unit IQ test (WISC-III) and the WIAT screener; both teenager and parents are administered the teenager diagnostic instrument (K-SADS Affective Disorders Module, and if qualifies for MDD, the remaining portions of the K-SADS-PL interview will be performed). Parents are asked to complete an in-depth questionnaire about demographics, the teenager's developmental history, family, and treatment background. It is estimated that the B1 and B2 visits will each take about 2.5 hours.

Note: Because the K-SADS-PL at Gate B presages the K-SADS-P MDD module at Gate C and all subsequent assessment visits, and in turn logically informs the CDRS-R also administered at baseline, **the K-SADS is to be administered by the individual who will later become the IE when the patient is randomized.**

At sites where it is required for blood to be drawn before study entry, for example, a serum pregnancy test in females, a consent for blood to be collected may be obtained at the B visit.

(3) Between Gate B1 and B2 (described below) the study team will review all information to date. Teenager and family will be rated in detail against all inclusion and exclusion criteria. If it is determined that all eligibility criteria are not met, the Gate B2 visit will be used as the point to present the reasons for ineligibility to participate in the study. At this point, the standardized written referral materials will be provided. Note that the site has no obligation to provide other than a verbal summary of information obtained as part of the Gate B evaluation.

(4) Gate B2. It is the intent of the study to enter children with a primary diagnosis of MDD and to avoid over-diagnosing MDD in cases where such a diagnosis may be confounded by cultural, ethnic, minority, socioeconomic or developmental status. Thus, the teenager's problems must be considered within the current context of such circumstances. To accomplish this, a **Gate B2** clinic visit by the teenager and parent(s) (or primary caretaker(s)) will take place for <u>all</u> subjects. During this visit, the case manager/ clinician will conduct a further **clinical interview** with the patient and his/her parents to review all diagnostic data as well as clinical, social and treatment history data gathered. At this visit, it must be clear on clinical grounds that <u>duration</u> (six weeks) and <u>pervasiveness</u> (depressed mood and/or anhedonia more often than not in two of three settings: at home, school and/or with friends) criteria are met.

Any outstanding or vague issues will be verified and/or clarified, including but not limited to other diagnoses or medication the teenager may have received in the past; other illnesses; suicide attempts or abuse; and the impact that other circumstances such as cultural, ethnic or minority or economic status and language difficulty, may have on the teenager's eligibility for the study.

At those sites where a urine pregnancy test is not acceptable, blood will be drawn for a serum pregnancy test and mental status will be assessed (if not done at Gate B1).

If the B2 interview uncovers a previously unknown exclusion criterion (e.g., suicidal behavior), the clinician will use the B2 interview to explain why the teenager is not eligible for the study. Families who are found to be ineligible or decline to participate will be given a verbal summary of the measures collected thus far and the standard referral list of mental health providers. No formal treatment recommendations will be made, but general suggestions about type and availability of treatment are appropriate.

If, after the B2 interview, the subject meets all inclusion and does not meet any exclusionary criteria, then the study entry process will continue, and teenager/parents will be given an appointment for the Gate C1 Baseline Assessment visit. If there is a discrepancy (e.g., K-SADS gives diagnosis of MDD but clinician disagrees or vice versa), the decision for inclusion or exclusion of the teenager in the study should be discussed and resolved at the site level, with referral to the cross-site Caseness Panel for final decision as needed

(5) Adjunctive Services and Attrition Prevention (ASAP) Before Randomization

After consent is obtained from the family at Gate B, the responsibility for treatment may fall to the study (if initiated by subject's family) until the point of randomization or dropout before randomization. To provide necessary contact during the interval between Gate B and randomization, the treatment teams at the sites will already have assigned a case manager. In many cases, the case manager will be one of the therapists who will later serve as therapist for those assigned to CBT-only and the combined groups. Before randomization, the case manager will: (1) maintain weekly telephone contact; and (2) provide, on an as-needed basis only, up to two crisis-driven treatment sessions consisting of supportive, non-directive counseling (as described in the ASAP Manual). The overall aim during this time period is to meet clinical responsibilities to the patient by responding appropriately to emergent situations, limit treatment contamination from additional treatment outside the study setting and from systematic behavioral treatment or medication treatment by the study staff, and to prevent attrition.

In general, if family members other than the subject are in need of additional treatment (e.g., maternal depression, paternal alcohol abuse), appropriate referrals may be made to clinical services outside of the study setting. Parent interventions will be tracked under ASAP procedures as specified in the ASAP manual. For problems of the study teenager, e.g., if a school problem is involved, the study team may contact the school, let them know they are aware of the problem and state when assessment will be completed so that treatment can start. All subjects will be treated the same during this time period, i.e., not according to treatment group as they will not have been randomized at this point.

(6) Baseline Assessment (Gate C1)

The Baseline Assessment visit, which is estimated to take about 4 hours, consists of ratings and assessments for the parent about the parent, about the teenager and about the family and parent/teenager relationship; for the teenager about the teenager and about the family and parent/teenager relationship.

The Baseline Assessment (Gate C1) is completed only for subjects who meet full entry criteria at Gate B1 and B2. The assessment visit will take place at the clinic and is set to occur immediately before randomization is revealed at the Orientation Visit. To ensure stable MDD, Gate C1 includes the requirement that the teenager meet MDD criteria on the K-SADS module and obtain an IE rated CDRS-R score $\geq$ 45.

Special attention should be given to whether a primary caregiver or non-primary parent with a BDI > 20 should be considered for referral for evaluation of major depression. Such a referral will be managed under ASAP procedures and recorded on the ASAP Log.

In the unlikely event a subject meets K-SADS MDD criteria at Gate B, but does not meet CDRS and/or K-SADS criteria at Gate C1, the site may defer the remainder of the Gate C baseline evaluation for one week. If on reevaluation one week later, the subject meets all in- and no exclusion criteria, then he/she

is study eligible. If he/she does not, then this patient should be referred to community treatment per standard TADS procedures.

Since the medical history is done at B (1 or 2), the physical examination, including Tanner staging, can also be done at Gate B or may be deferred to C1 at the site and patient option.

Note: To remain consistent with current standard-of-care, other than a pregnancy test, no screening laboratory tests are required in TADS. However, if the medical history or physical examination uncover medical illnesses that require further medical evaluation **and** that might represent, if present, an exclusion criteria or a confounding factor for MDD (for example, hypothyroidism or severe anemia), the patient should be referred for appropriate medical evaluation before moving to the Gate C2 orientation visit.

3.4.4. Random Assignment to Treatment

After the completion of the Gate C1 Baseline Assessment, the randomization procedure takes place. Randomization will be done at the subject level; that is, as each teenager completes the Gate C1 Baseline assessment, s/he will be randomized to a group. All four groups are equally possible for each teenager. The actual procedure is best described as a stratified randomization, with randomized permuted blocking within each stratum. Stratification variables are site and gender.

After Gate C1 is completed, the site coordinator will call the randomization phone number at DCRI to enroll a patient and receive a treatment assignment. Patients who receive a drug assignment will be issued a kit number and sites will retrieve that kit from their pharmacy inventory. That drug kit number will be linked to patient identification number. The treatment (whether placebo or active drug) will be blind to site personnel, the patient, and the pharmacist. Although the site coordinator will now know the subjects treatment assignment (but not if active or placebo pill), so as not to bias the C2 Orientation Visit discussion, randomization assignment will not be revealed to the clinician (the PI or a designated Co-I) conducting the C2 Orientation Visit in advance of the final review of the consent procedure that takes place at Gate C2.

Pre-Randomization Refusers

Although sites are informed of treatment assignment immediately after the Gate C1 Baseline Assessment, subjects are not informed of treatment assignment until their Orientation Visit. Therefore, subjects who refuse to continue before learning their group assignment at the Orientation Visit ("pre-randomization refusers" as distinct from “drop outs” who withdraw consent following randomization) will not be counted as randomized into the study.

Hence, subjects are considered **randomized** when they learn of their treatment assignment at the Gate C2 Orientation Visit. Subjects who have not yet had their randomization assignment revealed at the Orientation Visit are considered **study eligible** but not randomized. Stated differently, any potential subject who has completed any of Gates A, B1, B2 or any portion of C but is not randomized (e.g., told of his or her treatment assignment) to a treatment group is NOT considered to be a TADS subject for the purpose of the ITT analyses. Specifically, study eligible subjects who withdraw consent before randomization or who for any other reason are not randomized will not be included in the ITT or secondary analyses. A database of this pre-randomization sample will be established, to assess the generalizability of the eventual study sample.

To the extent possible, subjects who refuse participation immediately after the Orientation visit but before treatment is initiated or very early in treatment (i.e., within 2 weeks) may be "replaced" only in the sense that attempts will be made to enter additional subjects (over and above the 48 per site) to be randomized. That is, there will be an attempt to augment the overall study sample size but these additional subjects will not be entered into the same group assignment as the subject who dropped out; but will be randomized to one of the four study treatments.

Emergency Unblinding During Stage I

In the event of a patient emergency that requires unblinding a patient assigned to the Stage I pills only condition, the site will contact the DCRI Hotline available 24 hours/day. The hotline technician will in turn page the CC clinician on call for TADS emergencies (usually Dr. March) and will remain on the line while Dr. March and the site representative discuss the patient emergency. If after discussion, a decision is made to unblind the patient, the clinician will immediately authorize the DCRI hotline technician to reveal the patient's treatment assignment after the clinician has left the call. In all cases, patient safety takes precedence. Since this is best determined by the clinician who has evaluated the patient and who ultimately is responsible for that patient's care, if the CC and the site disagree, the site decision to unblind the patient will be binding on the CC.

(7) Orientation Visit (Gate C2)

Although the site obtains group assignment immediately after the Gate C1 Baseline Assessment visit, the assignment is not immediately revealed to the subject and family. Rather, a separate "Orientation Visit" conducted by the Principal Investigator or one of the two site Co-Investigators according to a pre-defined script is scheduled for the purpose of establishing randomization. **The Orientation (C2) visit may occur the same day as the C1 Baseline visit, but must occur within 1 week, depending on site procedures and subject preference.**

This visit has five goals:

- First, to reconfirm the rationale for treatment (and TADS eligibility) in the mind of the patient and parent, the PI will briefly review the results of the Gate B and C evaluations in the context of the goals of TADS.
- Second, to make sure that patient and parent understand the obligation that the TADS team has to them, the PI will review (1) each of the 4 treatment groups, (2) the TADS assessment schedule and (3) the provision of end of treatment recommendations.
- Third, to make sure that the patient and parent understand their participation in TADS, the PI will discuss the patient's responsibilities, including the expectation that the patient will maintain-treatment within the assigned arm and completing all assessment visits irrespective of treatment status.
- Fourth, the PI will review with the parent/teenager TADS provisions for suicide, including establishing a no suicide contract, and confidentiality procedures for drug use/abuse and pregnancy.
- Fifth, having reviewed the four treatments and ascertained that the patient and primary caregiver understand and are willing to accept randomization, the PI will reveal group assignment to the family after which their reaction will be recorded.

If other than the person who reveals group assignment, the primary therapist**,** who will be the central contact point for the family for the remainder of the study, will be introduced, treatment procedures and requirements will be reviewed, and a visit to begin treatment will be arranged. The primary therapist will be the cognitive behavior therapist for CBT or COMB groups and the pharmacotherapist for pills only. Depending on the outcome of the randomization procedure, the primary therapist may or may not be the same person as the temporary case manager up to this point. (Refer to (5) above for discussion on case manager.)

The primary therapist should review the TADS no suicide procedures in the context of the risk for suicide in MDD. Whether or not suicide is a current issue for the patient, both patient and parent will then be asked to agree to a no suicide contract.

The primary therapist will then review the confidentiality provisions, which will be uniform across sites unless the site IRB or local or state law requires specific deviations. The patient/family should be told that confidentiality will only be broken when dangerousness (defined as threat to life) to self or others is at issue. Hence, parents will not be informed of drug use or abuse unless it imposes potentially life threatening consequences (e.g. heroin use), but will be informed of dependence. Similarly, the patient

will be strongly counseled to discuss pregnancy with the parents, but TADS staff will not and cannot require disclosure under most state legal statutes. Note that we will track menstrual cycles in females at Tanner II Self Report and above to monitor for pregnancy after the initiation of the study and as a potential mediator of treatment outcome.

Failure to agree to the no suicide contract or confidentiality provisions will be sufficient reason to exclude the patient from TADS.

Finally, the Orientation Visit ends with a summary of immediately upcoming TADS treatment and assessment procedures in the patient's assigned arm, including introducing the Affective Disorders Screen (ADS), and acquiring information from patient/parent about their schedules to be used in scheduling the initial treatment visits if not already set to immediately follow the Orientation Visit.

Summary measures will be made available to the CBT therapist and/or pharmacotherapist at the time of the Orientation Visit. No access will be granted to any after-baseline data other than measures specifically intended for ongoing clinical treatment monitoring, according to the various treatment protocols.

(8) Issues Pertaining to Timing of Gate C2 and the Initiation of Treatment

Treatment Start

For all intents and purposes, the Orientation Visit (Gate C2) is considered as the "start of treatment" (i.e., the Stage I "clock" begins at this point, which is labeled T0). T0 is defined as the point at which the patient and family are informed of their assigned treatment (Pill, CBT, Combo) during the Orientation visit.

The first week of treatment is labeled week 1, which begins at T0; visits are scheduled by week of treatment. Visit 1 takes place during week 1 and denotes the start of one week of treatment, whether it be with pill, CBT or Combination. Stated differently, irrespective of the actual number of sessions attended, all patients will be considered to have had an amount of treatment in weeks equal to the number of weeks completed since T0. For example, at the start of week four, a patient on FLX would have completed three weeks of FLX and be ready to move from 20 to 30mg as scheduled at pharmacotherapy visit 4, depending on CGI score and side effect profile, at which time he/she would be considered to have received 4 weeks of treatment. Similarly, at the week 12 visit the patient would be considered to have completed 12 weeks of treatment, with determination by the clinician regarding whether or not he/she moves into Stage II as a partial or full responder.

To guarantee that patients receive a full twelve weeks of treatment in Stage I, the following **treatment initiation schedule** should be followed if at all possible.

- For patients in pills only condition, the first pharmacotherapy visit should immediately follow the C2 Orientation Visit.
- For patients in the CBT only condition, the first CBT visit should immediately follow the C2 Orientation Visit.
- For patients assigned to Combination treatment, the first pharmacotherapy and the first CBT visit are best scheduled back-to-back immediately following the Orientation Visit. Alternatively, depending on feasibility considerations, the first CBT visit should immediately follow the C2 Orientation Visit, with the first pharmacotherapy visit to follow within two or three days when the patient returns for the second (week 1, visit 2) CBT visit. This schedule is preferable because there are two CBT visits in week one, which makes CBT more difficult to schedule than pharmacotherapy.

Although convenience may dictate that assessment and treatment visits occur on the same day, the assessment schedule is independent of the treatment schedule. For example, the week 12 assessment

visit occurs some time during week 12 irrespective of whether the patient has completed all of the scheduled Stage I treatment visits.

End / Beginning of Stage

Treatment ends for a specific stage after the last visit for that Stage and begins with the first visit of the next Stage. For example, Stage I ends and Stage II begins after the end of the week 12 Stage I visit and the Stage II week 13 visit, respectively.

Relationship between Visit and Assessment

Assessments can be conducted on the same or different days from treatment visits, depending on feasibility considerations. If the assessment and treatment visits are scheduled back-to-back, **the IE visit (and preferably all other assessments too) should come before the treatment visit** in order to not bias the subject's responses because of recency effects from the treatment session. **In this regard, the clinical staff (all except the IE supervisor and study coordinator) remain blind to the IE ratings and, of course, the IE is blind to all clinical activities by the study team.**

Because the patient may exit the trial at week 12 or at any point in TADS where continuing TADS treatment would be unethical, treatment providers and study staff must be instructed (1) to remind patients not to reveal treatment status or (2) not to coach parent/patient regarding their responses to the IE or on any other interview or self-report assessment measure.

Who Must Attend Treatment and Assessment Visits

Patients are expected to attend all treatment and assessment visits. Parents are expected to attend all entry Gate Visits and treatment visit number one for both CBT and medication. Parents are expected to attend the scheduled parent visits in the CBT conditions. With these exceptions, parent attendance at treatment visits will be adjusted clinically by the site therapist in consultation with the supervisor for the specific treatment conditions.

4. Treatments - Descriptions

TADS treatment manuals provide a clear rationale for the treatment modality in question and carefully guide treatment. Specifically, (1) medication will be given according to standard procedures detailed in the Pharmacotherapy Treatment Manual, (2) CBT will be administered according to standard procedures detailed in the CBT Treatment Manual, (3) patients receiving COMB will follow procedures for CBT and medication management beginning simultaneously according to procedures outlined in the Pharmacotherapy and CBT Treatment Manuals, and (4) provision of adjunctive services to prevent subject attrition are presented in the Adjunctive Services and Attrition Prevention (ASAP) Manual.

4.1. Pharmacotherapy

In this section, we outline general procedures for pharmacotherapy, which are fully specified in the Pharmacotherapy Treatment Manual.

Patients will have one adolescent psychiatrist throughout the study who, in addition to monitoring clinical status and medication effects, will offer general encouragement about the effectiveness of pharmacotherapy for MDD. Patients will be seen for six office visits and will receive up to six phone calls during Stage I.

Table 4: Visit Procedures

TIMING	TOPIC
Beginning	Welcome
Middle	Review MDD symptoms using ADS Assess compliance with medication Assess side effects General encouragement to expect that medication will help reduce MDD symptoms
End	Set medication for the coming week Provide medication diary

Visit Schedule

Visit procedures are outlined in Table 4; the Stage I FLX dosing and visit schedule is outlined in Table 5. At each 20-25 minute medication visit, the psychiatrist will inquire about side effects before initiating (visit 1) or adjusting (later visits) medication. Fluoxetine and matching PBO in 10 mg doses will be packaged in bottles containing sufficient medication at a maximum of 40 mg per day until the next office visit.

Table 5: Stage I Dosing/Visit Schedule

Week	Visit*	FLX Dose**
1	Office	10 mg
2	Office	20 mg
3	Phone	20 mg
4	Office	20-30 mg
5*	Phone	20-30 mg
6	Office	20-40 mg
7*	Phone	20-40 mg
8*	Phone	20-40 mg
9	Office	20-40 mg
10*	Phone	20-40 mg
11*	Phone	20-40 mg
12	Office	20-60 mg

*All phone visits except week 3 are optional if patient is at CGI-S of 1 or 2

**Dose increases may be deferred or doses may be adjusted downward for side effects only.

Dosing Schedule

To best reconcile dose-response and time-action effects, TADS uses a flexible dosing schedule (Table 5) that is dependent on pharmacotherapist-assigned CGI-S score and the ascertainment of clinically significant side effects. Relative to normal functioning for an age, race, gender and community matched peers, the CGI-Severity (CGI-S) score will be anchored as follows: 1=normal, not at all ill, 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, 7=among the most extremely ill. Response requires CGI-S of 1 or 2; partial response a 3; and non-response a 4 or worse.

The dose of FLX may be increased by 10 mg at week 4 and 10-20mg at weeks 6 and 9 according to the following CGI-S schedule.

- If the CGI-S score = 1 or 2, no change in dose.
- If the CGI-S score = 3, the clinician has the option to leave the dose the same or increase it to the next higher dose to account for time-response considerations (the expected time to onset of benefits or resolution of side effects).
- If the CGI-S score is $\geq$ 4, the pharmacotherapist (absent limiting side effects) must increase to the next higher dose in a 10 or 20 mg increment, depending on the week of treatment and on the presence of dose-limiting side effects.
- In partial responders, the dose may be increased by 10 or 20 mg, depending on the starting dose and side effects, to a maximum of 60 at the week 12 visit.

Dose increases may be delayed or doses reduced for clinically significant side effects, e.g., side effects producing both distress and dysfunction, for which the clinician and the patient/parent believe dosage stabilization or reduction is indicated. All adverse events (e.g. moderate side effects or above) recorded

on the AEL that are thought likely to be side effects should prompt careful consideration regarding delaying a dose increase or decreasing the dose of study drug.

Except for the week 3 phone visit, which is mandated, all phone visits are optional for patients at CGI-S scores of 1 or 2 at the previous office visit. Conversely, phone visits may be converted to clinic visits when the clinician concludes that patient monitoring requires it. Dose increases that were previously delayed because of side effects may be agreed to by phone; all other dose increases require a clinic visit.

Integration with CBT for Patients in Combination Treatment

With the exception of pills-only condition in Stage I, treatment providers are not blind to treatment status. In fact, sites are expected to review the clinical status of each teenager in TADS in rotation at weekly TADS team meetings. This offers the opportunity to integrate aspects of CBT and medication treatment for those children assigned to COMB. For example, patients at week 6 who are partial responders could escalate in dose or stay the same, with the decision in part turning on how well the CBT therapist believes the patient is progressing in CBT.

To allow limited integration between medication management and CBT, we will use the following decision rules:

1. CBT is functionally independent of medication management, e.g. no decisions regarding the CBT protocol depend on decisions regarding medication management.
2. For all dose increases other than those depending on a CGI-S of 3, the protocols for administering medication and CBT are functionally independent.
3. When the CGI-S = 3, e.g. partial response, the pharmacotherapist should consult with the CBT therapist at the weekly TADS team meeting, where it is expected that all TADS patients will be discussed in rotation, or at another time of mutual convenience. This discussion, the goal of which is consensus between the pharmacotherapist and CBT therapist regarding FLX dosing, should center on the following: (1) whether the patient is making good use of CBT and, in that context, (2) whether the change trajectory for MDD symptoms over time suggests that a dose escalation is warranted or whether it would be prudent, especially if side effects are bothersome, to delay a dose increase until it is clearer that the patient is not progressing as expected for a hoped for treatment responder. In the unlikely event of disagreement, the pharmacotherapist will decide the dosing strategy to be followed.

Dosing and Visit Schedules in Stage II

All FLX, CBT or COMB patients with a clinician assigned CGI-S score of 1, 2 or 3 (e.g. partial or full responders) will continue into Stage II. Patients with a CGI-S score of 1 or 2 at the end of Stage I will continue on the same dose of FLX but at a reduced visit schedule during Stage II. As shown in Table 6, if the end of Stage I clinician CGI score is 3, indicating partial response, then the Stage II dose may be increased at week 14 and 16 by a minimum of 10mg and a maximum of 20mg, depending on the presence of dose-limiting side effects. The maximum Stage II dose is 60mg. For example, if a subject ended Stage I as a partial responder at 40mg, the pharmacotherapist could increase the dose to 50 or 60mg, depending on whether side effects were present. For example, if minor side effects were present, the pharmacotherapist might elect to increase the dose to 50mg rather than

Table 6: Stage II Dosing/Visit Schedule

Week	Responders*	Partial	FLX**
13	--	Phone	20-60mg
14	--	Office	20-60 mg
15	Office	Phone	20-60 mg
16	--	Office	20-60 mg
17	--	Phone	20-60mg
18	Office	Office	20-60mg

*Phone visits are optional for responders; mandatory for partial responders following a dose change.

**For partial responders, a dose adjustment upward by a minimum of 10mg and a maximum of 20 mg at weeks 13, 14 and 16 is permissible; otherwise, dose may be adjusted downward for side effects only. If the dose at week 12 is 60mg, no further dose increases are possible.

60mg. If the dose was raised to 60mg at the week 12 visit, no further dose increases are possible.

Dosing and Visit Schedules in Stage III

Stage III medication patients will be followed every six weeks with 20-25 minute medication visits. Other than downward adjustment of the dose for major or prohibitive side effects, no adjustments to the dosing regimen arrived at in Stage II are permitted. If a patient worsens in Stage III with either an associated clinical crisis mandating an urgent or emergent intervention or threatened attrition, a dose change in FLX may be undertaken using ASAP procedures.

Stage IV

With its long half-life, withdrawal symptoms are not problematic with FLX. Hence, medication can be discontinued abruptly in FLX treated patients at the end of Stage III if discontinuation is in fact recommended. Procedures for recommending follow-up care are specified in Section 4.5.

Pharmacotherapy with a Psychostimulant

Stable treatment with a psychostimulant is permitted under the following guidelines:

- Adderall or IR or sustained release methylphenidate or Dexedrine are permitted; pemoline and methamphetamine are excluded.
- Stable psychostimulant treatment means that the total daily dose has not changed by more than 25% during the 12 months preceding study Gate B consent. Drug holidays (e.g. weekends and vacations) are not considered as dose reduction.
- It is assumed that stimulant dose is optimized at study entry. No attempt should be made to optimize psychostimulant treatment, e.g. by adding doses, changing doses or switching to another stimulant. If changes in stimulant treatment are needed, these will occur through ASAP procedures.
- For patients in the CBT only condition, written agreement was obtained pre-randomization from the patient's prescribing physician to monitor psychostimulant treatment within the following parameters: (1) no change in psychostimulant dose is permissible without consultation with the CBT therapist, (2) no other psychotropic medication or recommendations regarding psychotropic medication are permissible and (3) no psychosocial treatment or recommendations regarding psychosocial treatments are permissible.
- If additional treatment for ADHD outside the TADS protocol becomes necessary on an urgent or emergent basis, such treatment will be provided as required under ASAP provisions and, if needed, by referral to community care.

4.2. Cognitive-Behavioral Therapy

CBT is a skills-based treatment based on the assumption that depression is either caused by or maintained by deficient social cognitive skills for coping with stress. Two major subsets of such skill deficiencies are depressive thought patterns and the lack of active, positively reinforcing behavior patterns. As with Pharmacotherapy, CBT will be guided in an individual CBT manual with an accompanying manual for parent and conjoint family sessions.

Personality is conceptualized as an interactive multi-directional system of behaviors, cognitions, and emotions.[92] Depression is manifested in each of the three components of the personality, but change is most likely to occur through interventions that modify patterns of behavior or patterns of cognition. Among the behavioral and cognitive skill deficits that may characterize a depressed youth are low levels of involvement in pleasant activities,[93] poor problem-solving and assertion skills,[94,95] cognitive distortions that negatively bias perceptions,[96] negative automatic thoughts,[97] negative views of self and future,[98] and failure to attribute positive outcomes to internal, stable, or global causes.[99] The role of the therapist, therefore, is to establish a working alliance with the adolescent and to help the adolescent learn new ways of behaving or thinking, which in turn reduce depressive severity and risk of relapse.

The approach taken to CBT in TADS has two salient characteristics: (1) it has both general or "required" skill-building sessions and optional or "modular" sessions for specific adolescents; and (2) it integrates parent and family sessions with individual CBT. Treatment is designed to improve the adolescent's ability to take active behavioral steps to cope with stressors, and to think in more flexible, realistic and adaptive ways in situations that could otherwise lead to depressive cognitions. Therefore, the required aspects of treatment include psychoeducation about depression and its causes, goal-setting with the adolescent, mood monitoring, increasing pleasant activities, social problem-solving, and cognitive restructuring. Modules, chosen jointly by therapist and adolescent, then address relevant social skill deficits of the individual teenager, such as problems in social engagement, communication, negotiation, compromise, or assertion. Family sessions similarly include psychoeducation for parents about depression and about CBT for the adolescent, and then more flexibly focus on identified parent-adolescent concerns, as described below.

Active treatment in Stage I will begin with a joint parent-adolescent Rationale and Goal-Setting session that includes psychoeducation. Treatment then includes 12 sessions of either individual or family cognitive behavior therapy for the adolescent in the 12 weeks of treatment. All sessions are 60 minutes unless otherwise stated. The first session is held during Week One. Therefore, there are two sessions in that week only: the Rationale session and the first individual session. Other CBT sessions in the first six weeks are individual, but may include a parent "check-in" at the beginning to mirror standard clinical practice. A minimum of one and a maximum of three sessions during the second six weeks are family (parent-adolescent) CBT for the adolescent. If there are compelling clinical reasons, therapists may request to allot more sessions in the second six weeks to family CBT by submitting this request to the weekly CBT supervisors' call.

There are also two psychoeducational sessions for parents only, during Weeks Three and Five of Acute Treatment. These are to be scheduled back-to-back with individual adolescent sessions, so that the family is asked to come to the clinic only once per week. Total duration of each of these sessions and their adjacent adolescent session is 90 minutes. Taken together, all Acute Treatment CBT (Stage I) consists of 14 hours of clinical contact in 12 weeks: 2 hours in Week One, 90 minutes in Week Three and Week Five, and 1 hour in each of the other 9 weeks.

In Stage II maintenance treatment, sessions will be every other week for Stage I full responders (CGI-S = 1 or 2) and weekly for Stage I partial responders (CGI-S = 3). For full responders, sessions will focus on generalization training and relapse prevention; no new skills may be introduced. In accordance with the goal of flexibly targeting treatment to problem areas that are patient-specific, sessions for partial responders will continue to focus on CBT modules that are deemed clinically relevant by the patient's therapist. In this regard, these sessions may include any skills that are included in the manual for Stage I, which the therapist considers indicated for this particular teenager. Up to three sessions in Stage II may be family CBT for the teenager, without further requests by the clinician to the CBT supervisors' conference call.

As noted earlier, parent-teenager conflict is a risk factor for depression, poor treatment outcome and relapse after treatment. Including a parent component in CBT is thus justified on an ad hoc basis, and because at least preliminary evidence suggests that parent + teenager treatment may be somewhat more effective than treatment directed at the teenager alone.[92] In the proposed study, we will provide parents with psychoeducation in the Rationale session and in two parent sessions in the first six weeks of acute treatment.

These three sessions will cover material generally relevant for cases of adolescent depression: (1) psychoeducation about the characteristics and possible causes of depression; (2) rationale for CBT; and (3) characteristics found in many families of depressed adolescents (high standards, low rates of positive affective reinforcement, and low rates of positive family activities). We will provide parents a total of up to six sessions during Stage I. The remaining family sessions will be tailored to the needs of the individual family and adolescent, with modules taken from the family therapy manual that are pertinent

to the specific family. We will include in the family manual, skills-training sessions on such topics as communication, negotiation, family problem-solving, and parental affect regulation

In Stage II, responders will have three CBT sessions; partial responders will have six sessions, the content of which (including extent of family involvement) will reflect the tailored approach to CBT reflected in Stage I weeks 6-12.

In Stage III, CBT therapists will provide booster sessions every six weeks targeting generalization training and relapse prevention strategies.

4.3. Combined Medication and CBT

This treatment arm will consist of all the components from both the medication-only and CBT-only arms. To simplify the protocol and to limit the possibility of site-by-treatment interactions, CBT and medication management will begin simultaneously and proceed according to procedures specified in the CBT and Pharmacotherapy manuals.

Consistent with the multidisciplinary approach taken in TADS, CBT and medication appointments will occur during the same visit in the same physical location to reduce patient/parent inconvenience and increase compliance.

With the exception noted earlier regarding medication adjustment, CBT and medication management are conducted according to protocols that independently escalate the intensity of treatment over time and there are no treatment dependencies between CBT and medications--i.e., changes in the nature or intensity of CBT or medication management do not depend on the other treatment. As outlined above, the only exception to this rule involves flexibility in medication dosing for patients showing a CGI-S of 3 in Stages I and II, where the pharmacotherapist in conjunction with the CBT therapist may elect to defer a medication increase when it seems likely that the patient is making good progress in CBT making a dose increase unnecessary.

4.4. Stages II and III: Maintenance and Extended Treatments

Placebo (PBO) Subjects

At the end of Stage I, PBO and FLX patients will be informed of their treatment assignment. Patients on PBO who improved over the course of the 12 weeks (clinician assigned CGI-I of 1 or 2), will be offered phone follow-up during the next three months, but no further treatment will be given. If these PBO patients relapse within 3 months, they will receive 12 weeks of open FLX, CBT or COMB treatment, depending on patient preference. PBO patients who did not improve during the first 12 weeks (CGI-I greater than 2, e.g. partial response or worse) will be enrolled in open FLX, CBT or COMB treatment, depending on patient preference, for 12 weeks. All PBO subjects will continue to be followed on the TADS assessment schedule for the entirety of Stages and IV and on the major assessment schedule only during Stages II and III.

All Others

At all points, TADS places the patient's welfare first. Hence, the clinician-assigned CGI-I score will determine whether a patient exits the treatment portion of the trial at the end of Stage I or continues into Stages II and III. More, specifically, at the end of Stage I, CBT, COMB and FLX patients who responded positively to treatment as indicated by an clinician-assigned CGI-I score of 1, 2 or 3 will enter the 6-week Stage II maintenance/consolidation phase followed by 18 weeks of Stage III maintenance visits every 6 weeks. Subjects will be seen by the same treating clinician that administered CBT (CBT and COMB groups) and/or medication (FLX).

Stage II pharmacotherapy visits will be biweekly or every third week visits (see Table 6), depending on response status, with responders continuing on their Stage I dosing regimen and partial responders advancing to 60 mg FLX as tolerated beginning at the week 12 office visit.

For responders to CBT, follow-up sessions will last 30-50 minutes, and will emphasize generalization training and relapse prevention following procedures outlined in the CBT treatment manuals following a reduced visit schedule, i.e. no new skills may be introduced. Visits for partial responders to CBT, which will be individualized (problem-specific individual or family sessions as specified in the CBT manual) will last 50-60 minutes. Hence, the Stage I CBT agenda can be flexibly extended into Stage II (but not Stage III) for partial responders. Nonetheless, because Stage II CBT treatment is focused on tailoring CBT to residual symptoms, it naturally allows exactly this type of flexibility.

The assessment schedule is independent of the treatment schedule, which provides for the incorporation of feasibility into the overall outcome as is appropriate to an effectiveness study.

In Stage III, every six week medication visits will last 20-25 minutes; every six week CBT visits will last 50 minutes. All other treatment in Stage III, including additional CBT visits and medication adjustment will require ASAP procedures.

Patients will be instructed to adhere strictly to the maintenance visit schedule. Non-protocol psychotherapeutic treatment outside the study is disallowed during Stage II and III; similarly, treatment with any psychotropic drug (other than study drug or maintenance psychostimulant treatment) for any psychiatric indication is not permitted.

4.5. Non-Responders, Partial Responders and Stage III Debriefing and Referral Options

Assessments

Consistent with the intent of the ITT analyses, and agreed to at the Gate B consent and Gate C orientation visits, all non-responders and prematurely terminating subjects who receive open treatment outside the study will be asked/expected to return for the Full but not the Minor assessment batteries.

Non-response at the End of Stage I

Subjects with a clinician-assigned CGI-I score of 4 (no change from baseline) or worse at the end of Stage I will be considered non-responders and will be ineligible for the Stage II and III treatment components of TADS.

While having a more in-depth understanding of the teenager's history and past symptoms may lead to more accurate assessments of clinical improvement and symptom severity, knowing treatment condition can also influence these ratings. To balance these two competing imperatives (which roughly approximate external versus internal validity), the clinician assigned CGI-S score will determine the "dosing" algorithm in Stages I and II, the clinician-assigned CGI-I score will determine advancement from Stage I to Stage II, and the IE-assigned CGI-I score will determine response status for the purpose of the primary outcome measure. Although bias might be introduced by the clinician with respect to desire to continue treatment for reasons, such as the desire of the patient to continue with the doctor, not pertinent to the patients actual condition, matching TADS treatment procedures to actual practice took precedence over IE independence/blindness with respect to the decision to advance patients from acute to maintenance treatment.

For patients in CBT and pills conditions, the primary clinician is the cognitive-behavior therapist and the pharmacotherapist, respectively. For patients in COMB, the **primary clinician** is the cognitive-behavior therapist. However, it is expected that the CBT therapist and pharmacotherapist will jointly review each COMB patient at week 12 and whenever premature termination is under consideration to finalize the CGI-S and CGI-I scores. If the two disagree, the PI and the CBT and pharmacotherapy supervisors, having reviewed all available information, will make a final determination in consultation with the treating clinicians using a forced consensus judgment procedure in which disagreement is not allowed.

Using the End of Stage III recommendation procedures defined below, non-responders will receive whatever recommendation the treating site deemed clinically and ethically appropriate.

Non-responders at Other Times

Responders and partial responders may on occasion become non-responders during Stage II and III. Some partial responders (CGI-I of 3 on the clinician assessment) at the end of Stage II will be doing well enough to continue in treatment, with the expectation that TADS Stage III maintenance treatments will provide sufficient support that continued treatment in their assigned arm is justified. Others will be doing sufficiently poorly with respect to MDD and/or comorbid problems so that other treatments are clinically indicated. Some patients may exhibit transient worsening at a minor or major assessment point as manifested by a CGI-I score of 4 or worse, but in the judgment of the clinician continued TADS treatment in the patient's assigned arm may still be warranted. As described below in the sections on premature termination and ASAP, these are clinical decisions that rest with the primary clinician, not with the IE.

Recommendations at the end of Stage III

There are no procedures for maintenance of treatment condition following the end of the TADS 9 month treatment period. Hence, ethical principles require that at the end of the 9 months of treatment, all participants be given recommendations for any indicated further treatment and appropriate referrals. To standardize this process across sites, we will use a standardized debriefing script. Briefly, this script will a) provide the family a chance to state any concerns or questions they have; b) provide a summary of progress, using clinical indicators; c) outline the possible available treatments, emphasizing those in the assigned treatment arm but also explaining the others; and d) make recommendations about appropriate continuing treatment.

In a standardized manner, each site will review each teenager's clinical status at 9 months, giving an end-of-treatment recommendation score across all functional domains including but not limited to MDD of 1, 2 or 3 as follows:

- Level 1: Participants with a summary CGI-S of 1 or 2 (normal or borderline ill) and who are otherwise well, i.e., do not need treatment for other disorders or problems, receive a recommendation to discontinue all treatment unless (1) in the opinion of the site team continued treatment is indicated, for example, because of a history of relapse or (2) there is a strong patient/family preference for continuing treatment
- Level 2: Those with a CGI-S of 3 (mildly ill) or who require other treatments will receive a recommendation (as appropriate clinically) to continue study-delivered treatment(s) for MDD and to add other treatments if necessary.
- Level 3: Those with a CGI-S of 4 or worse (moderately ill or worse, unusual by the end of 9 months of treatment) receive whatever recommendation the treating site deems clinically and ethically appropriate.

All end-of-treatment recommendations will be coded for data entry.

Families will be given a list of possible providers for the recommended treatment and will be told that a clinical report could be sent with the parents' authorization to any new treatment provider(s).

Similar procedures (i.e., a Level 1, 2 or 3 recommendation) will be used for premature termination at any point in the study.

During and End of Stage IV Recommendations

In Stage IV, TADS treatment will have been discontinued and patients will be assessed with the reduced battery at 3 and 9 months and with a major assessment battery at 6 months and at the end of one year. For the purpose of maintaining rapport (1) there will be a ventilation-format debriefing at the end of each assessment and (2) up to two ASAP sessions will be provided. The purpose of Stage IV ASAP sessions will be to assess the need for clinical services and to make the appropriate referrals and not to provide treatment services per se. Clinical problems for which parents or teenager ask for help will be responded to with sound

clinical advice based on knowledge of the patient and available community services. The standardized resource list of referrals for dealing with common problems supplemented by other recommendations as needed, e.g. neuropsychological testing, may be provided as needed.

Although the use of a passive follow-up design in this sample has certain limitations, it does allow the examination of several crucial questions. For example, it will be possible to determine if intensive treatment results in a change in subsequent outcomes, in terms of differential risk for recurrence of MDD, risk for MDD-related impairments, subsequent familial help-seeking and use of effective services, or perhaps in outcome differences that are mediated through changes in parenting and help-seeking practices. Because randomization will have been lost, all Stage IV analyses are exploratory with their primary heuristic value being hypothesis generation for subsequent studies.

4.6. On Call Schedule

Each site should have a daily on-call schedule in place, with a listing of the primary and back-up clinical staff members who will handle emergency calls.

As noted above, Dr. March or his designee will carry the TADS beeper for the CC.

4.7. Developmental Considerations

Recent evidence suggests that allowing flexibility in the implementation of psychotherapy protocols, within overall conformity to clearly articulated treatment goals and procedures, improves treatment outcome when contrasted with rigid, manualized treatments.[100] Thus we propose to promote developmental appropriateness in part by allowing flexibility in the treatments within the constraints of fixed session goals. More specifically, the therapist will adjust the level of discourse to the level of cognitive functioning, social maturity and capacity for sustained attention of each patient. Younger patients will require more redirection and activities; adolescents will be more sensitive to the effects of MDD on peer interactions, which in turn will require more discussion; cognitive interventions too will require adjustment to the developmental level of the patient. Similarly, patients whose MDD symptoms entangle family members will require more attention to family involvement in treatment planning and implementation than those without family involvement. Nonetheless, while the CBT Treatment Manual includes a strong emphasis on developmental sensitivity, the general format and goals of the CBT treatment sessions will be the same for all patients.

5. Training, Certification, and Quality Assurance

To ensure that all sites conduct the protocol in the same manner, quality assurance (QA) procedures that cover administration of both treatments and assessments are critical to the success of a large complex multicenter trial such as TADS. In particular, QA procedures are necessary to guarantee (1) consistent standardized administration of TADS treatments, and (2) reliability defined as consistent standardized ascertainment of the primary dependent measures. Without QA procedures, the potential for site-by-treatment interactions increases, with no *a priori* guarantee that such differences, if they occur, are not the result of divergent administration of the TADS protocol at the individual site level. Hence, by enhancing reliability of assessment and administration of treatment, QA procedures are essential to securing valid data and, ultimately, to interpreting the findings from the trial.

Before enrollment of study subjects commences, the CC trains site PIs, and CBT, PT, and IE supervisors from each study site on the protocol and study procedures. The training includes (1) study materials, (2) a five-day training session to be held at a location near the CC, and (3) certification of the site IE, CBT, and PT supervisors. Materials provided for review in advance of the group training session include treatment manuals, assessment administration booklets, and data forms. The agenda for the centralized training session includes (1) an overview of the study protocol, study organization, and staffing requirements; (2) detailed training on study procedures, including recruitment and screening, randomization, unblinding, early termination, regulatory requirements, study medication, adverse events, data collection procedures and quality assurance; and (3) training on the delivery of the CBT and PT interventions and administration of the study instruments.

The CC uses a "training of trainers" (TOT) model to train site supervisors so that they, in turn, train and supervise the IEs and CBT and PT clinicians at their sites. "Trained trainers" leave the centralized training with an inservice manual, IE manual, CBT manuals, and Pharmacotherapy manual (PTM) for use at their sites. By using a TOT model, TADS places QA procedures at the heart of site implementation of the protocol, thereby maximizing site attention and allegiance to QA while at the same time minimizing costs and administrative inefficiencies associated with centralized QA monitoring.

Trained supervisors send a minimum of three tapes of CBT sessions and two PT sessions with volunteer or TADS feasibility study patients to the CC for review for certification. Certification will be based on successful completion of a CBT/PT knowledge test and demonstrated ability to adhere to the treatment protocols as described in the TADS CBT and PT manuals. CBT and PT supervisors are certified by the CC prior to enrolling subjects into the trial at their sites.

Certified supervisors train clinicians at their sites on the content and procedures for specific treatment sessions and meet with the clinicians on a regular basis to review adherence to treatment protocols and to answer questions about session content and flexibility. CBT and PT sessions are recorded on audiotape throughout the trial. After each session, CBT therapists complete a checklist indicating the topics and skills that were introduced, reviewed or used in the session.

Review of a sample of taped CBT and PT sessions by site supervisors and by CC staff using structured forms to rate adherence, competence and flexibility are core elements of fidelity assessment in TADS. For the first subject treated by each CBT therapist, supervisors will review the recordings of six CBT sessions. Tapes of three sessions are reviewed for subsequent subjects. For PT clinicians, supervisors will review the audiotapes of three PT sessions for the first subject, and two tapes for each subsequent subject assigned to the clinician. The CC preselects a proportion of CBT and PT tapes for QA review using an algorithm designed to ensure variation in the focus, content, and types of sessions reviewed (e.g., individual, family, parent sessions) and to minimize the potential for selection bias. The QA tape selection algorithm also takes account of the need for meaningful clinical supervision of CBT and PT therapists at the sites by having site supervisors and clinicians select a proportion of the tapes for review. Over the course of the study, the CC will also review a 5% sample of taped PT and CBT sessions to monitor and evaluate treatment fidelity and quality. To identify problems early in the start-up phase of the trial, this 5% sample will be front-loaded, that is, more tapes will be reviewed from earliest sessions. CBT and PT therapists who receive unsatisfactory ratings for adherence or competence by site supervisors or CC reviewers for three sessions are not assigned additional TADS subjects.

Certification of site IE supervisors on the primary dependent variables requires that each submits to the CC a tape of two CDRS child and parent interviews and associated CGI ratings. Completed supervisor interviews and CGI ratings are reviewed by the CC for inter-rater agreement and quality of administration. Supervisor certification on the CDRS and CGI is based on achieving criterion-based levels of agreement between the site supervisor and CC raters. Certified supervisors train IEs at their sites to administer the CDRS and CGI. Site supervisors meet with IEs to review the quality and reliability of their taped interviews and CGI ratings. In addition, all supervisor-trained IEs must submit their first two interviews to the CC and meet the same certification standards that are required for the IE Supervisors. To minimize interviewer drift, IEs are sent recordings of CDRS parent and child interviews to score and to compute CGI ratings on a regular basis throughout the study. Inter-rater agreement between interviewers will be examined for the CDRS and CGI. Interviewers with discrepant scores will be provided with individual performance feedback.

Uncertainties regarding how to administer the protocols are certain to arise in a trial as complex as TADS. To add an additional level of QA, weekly to biweekly teleconferences are held for both CBT and Pharmacotherapy providers. Similar calls are held for the IE and for all protocol deviations using the ASAP rubric. Using the teleconference mechanism, a set of precedents will be established regarding how best to manage situations that call for flexible administration of treatment. In turn, this

set of precedents will contribute to the development of a cross-site common culture, which will insure that the treatments and assessments are administered in the same fashion at all sites.

6. TADS Timeline

6.1. Recruitment and Study Entry

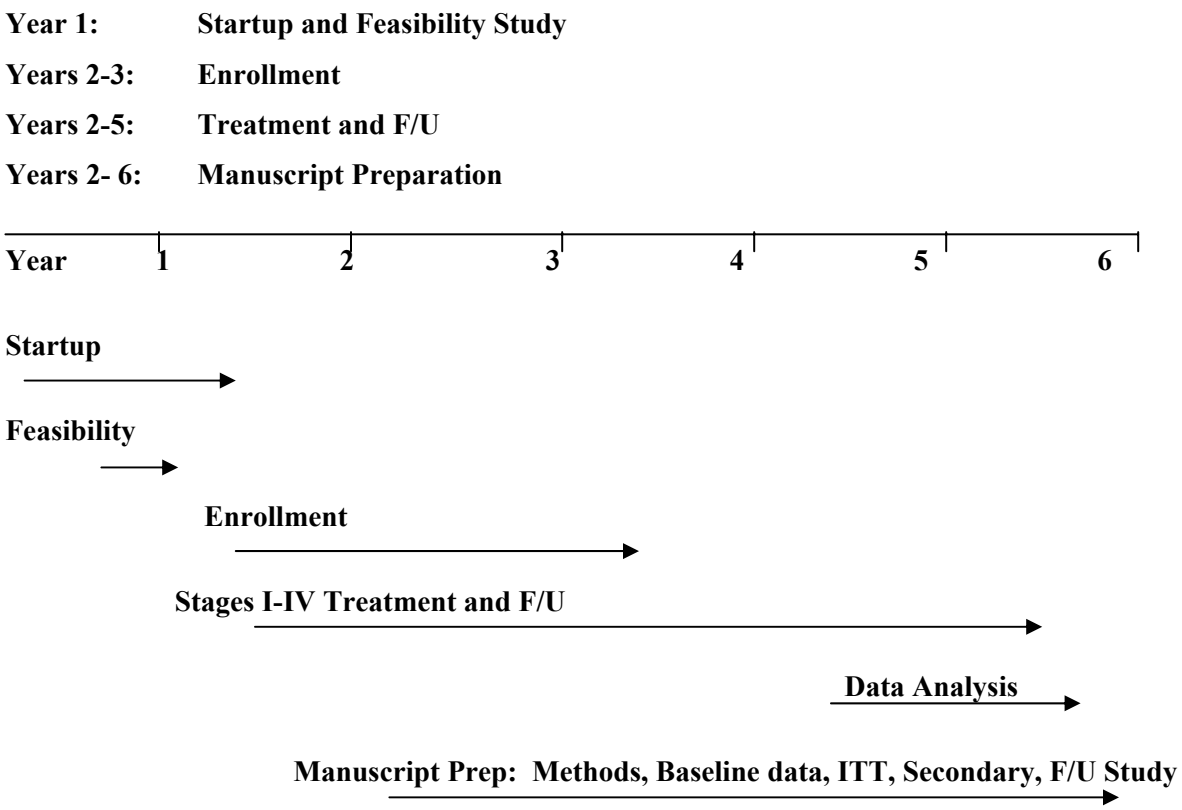
Figure 3 depicts the TADS timeline. Startup extends into the middle of the second of six years for the project, with enrollment beginning in March of 2000 and treatment occupying the years 2 through 4 and follow-up 3 through 5. Manuscript writing begins with a methods paper in year 2, moves to manuscripts on the baseline data in year 4 and concludes with core ITT and secondary papers in year 6.

Recruitment is defined as all phases before the Start of Treatment Orientation Visit (C2): Gates A (telephone screening), B (consent and diagnostic assessment), B2 (clinical interview), C1 baseline assessment and an optional additional studies visit and C2 for study orientation and treatment assignment.

In contrast to ADHD, where outcome is closely associated with academic and social performance and therefore is tied to the school year, it is not critical that the timetable for treatment accommodate the school year in patients with MDD. Hence, subjects will be recruited consecutively across years 2, 3 and4 of the study timeline. This allows 1.5 years to finalize the protocol and conduct training in assessment and treatment procedures and ample time toward the end of the study to complete data analyses and prepare publications.

The TADS timeline is diagrammed below:

Figure 3: TADS Timeline



6.2. Treatment Timetable

As specified in the respective treatment manuals, CBT and medication treatments begin and run concurrently. Except as noted for Combination Treatment, there are no treatment dependencies. As noted previously, the first week of treatment is labeled week 1; visits are scheduled by week of treatment. Visit 1 takes place during week 1 and denotes one week of treatment, whether it be with medication, CBT or Combination. Stated differently, irrespective of the actual number of sessions attended, all patients will be considered to have completed an amount of treatment in weeks equal to the number of weeks since the T0 orientation visit. For example, at the start of week four, a patient on FLX would have completed four weeks of FLX. Similarly, at the week 12 visit the patient would be considered as having completed 12 weeks of treatment and should be ready for the end of Stage I assessment that will determine whether he/she moves into Stage II. Consistent with good clinical care, patients move sequentially through Stages I to III with no interruptions.

7. Assessment Instruments

7.1. Screening Instruments

Gate A Screening: Screening Form

Information obtained via telephone or face-to-face interview by an experienced telephone screener, preferably a masters or doctoral level clinician. Purpose is to screen out obviously ineligible subjects (e.g., age, grade, on prohibited medication) and to include potentially viable subjects at this point so as

not to over-exclude. The Gate A screen will set up or initiate procedures to set up the Gate B appointment.

Gate B In-Person Visit:

Purpose is to explain entire study to teenager and family and to obtain written consent and assent; to determine final eligibility against all study inclusion and exclusion criteria and diagnosis.

Completed by parent and teenager:

- Orientation to study
- Written consent and assent (after discussion) witnessed by PI or Co-PI)
- K-SADS-PL for Affective Disorders and, if qualifies, the remaining modules of the K-SADS-PL (Parent and teenager separately)
- Developmental, Family and Treatment Background Questionnaire (Parent only)
- Teen's medical history

Completed by teenager:

- Written assent (after discussion) (witnessed by PI or Co-PI)
- 2 subunit WISC-III (IQ test)
- WIAT basic reading screener
- Physical exam and Tanner Staging

Between Gate B and B2 (Can be same day at site option): PI/Site Team will review all background, treatment history and study eligibility criteria.

Gate B2 Clinical Visit (Can be same day at site option): Separate clinical interview with teenager and parents to be as certain as possible of diagnosis, to assess mental status and review background and treatment history data to date and to consider all relevant circumstantial factors.

Necessary For Caseness: Consensus (parent and teenager) K-SADS primary diagnosis of MDD and no exclusionary diagnoses **AND** agreement of diagnosis by clinician after interview of parent and mental status of teenager.

Gate C1 In-Clinic Baseline Assessment: Completed at the first "protocol" assessment, just before randomization to treatment. Only children and families who meet full entry criteria will receive this battery of assessments.

Gate C2 In-Clinic Orientation Visit: No assessments completed at this visit; however, the Treatment Assignment Reaction (TAR) is completed to document teen and parent reaction to treatment assignment.

Throughout The Study*:

Completed by CBT Therapist:

- All contacts CBT Session Checklist
- All contacts Affective Disorders Screen
- All contacts CGI
- All contacts CGAS
- All contacts Treatment note
- All contacts CBT Table

- As needed ASAP Log
- As needed Adverse Event Log (AEL)
- As needed Serious Adverse Event Form

Completed by Pharmacotherapist: (in addition CGI forms)

- All contacts PT Session Checklist
- All contacts Affective Disorders Screen
- All contacts Medication Count Log
- All contacts CGI
- All contacts CGAS
- All contacts Treatment note
- All contacts PT Table
- As needed ASAP Log
- As needed Adverse Event Log
- As needed Serious Adverse Event Form
- As required Treatment Blindness
- As required Medication Accountability/Dispensing Log

Completed by Pharmacotherapist at Phone Session:

- All phone contacts PT Phone Session Checklist

Completed by Other Staff: (Supervisors, Coordinators, Aides)

- As needed Concomitant Medication Log
- As needed Concomitant Treatment Log
- As needed ASAP Log
- As designed Adherence/Fidelity Forms
- As required Medication Accountability/Dispensing Log

*Contacts means scheduled weekly visits (it does not include phone contacts)

All time frames of reference for all scales at all major evaluation points are "within the past week" UNLESS noted otherwise.

Hierarchy of Parental figures

General Principle: Teenager is asked to refer to only one "set" of parents, even though more than one "set" of parents may be asked about the teenager. All scales must be completed on site by the "primary" caregiver independently of the patient, not in consensus.

If teenager's primary home is with two parents (or primary caretakers) (regardless of whether both are biological parents), both may participate in treatment but the parent questionnaires should be completed by the primary caregiver unless the instructions specify both parents (c.f. Conners Adult ADHD Rating

Scale). If there is also a biological parent not living in the primary home but whom the teenager regularly sees/lives with (e.g., divorced father with whom teenager spends weekends), that parent may be invited to be a participant in the study, if the primary caretaker(s) agrees. However, to avoid confusing the teenager, the teenager's questionnaires refer only to those "parents" in the primary home.

If a teenager's primary home is with only one parent (or primary caretaker) (regardless of whether that person is a biological parent), parent questionnaires should be completed by that person and the teenager's questionnaires refer to that person. If there is also a biological parent not living in the primary home but whom the teenager regularly sees/lives with (e.g., divorced father with whom teenager spends weekends), the teenager's questionnaires should refer to the home setting although the outside parent may be invited to be a participant in the study, if the primary caretaker(s) agrees.

7.2. Assessment Schedule During Treatment

A descriptive list of all instruments and forms to be used in the trial is provided in **Appendix C**. **Appendix D** lists all measures and forms completed for each patient and the domain of interest. We propose to use study measures covering all important domains of outcome specified in the RFP. Additionally, several trial management and administrative forms must be completed by site staff to assess adherence to the protocol and to address other fidelity and quality assurance issues. Where possible and practical, given cost factors, we employ multiple raters and measures across symptoms and across settings. These measures will be obtained at Baseline and periodically throughout the study.

With the exceptions noted below, all TADS subjects are expected to complete all assessment points. The only patients who are not expected to return for major assessments are those who withdraw consent, die or are lost to follow-up. As noted in the ASAP section covering “dropping out,” continued treatment in TADS is contingent on participating in the assessment portion of the study, e.g. if the patient withdraws consent for assessment, treatment ends. This is distinct from poor cooperation, where only some assessments are completed but the parent and/or subject indicate willingness to continue with assessments. PBO patients will complete only full assessment points after week 12. Patients who terminate prematurely will complete only full assessment points after their premature termination.

7.3. Dependent Measures

Tables 7 and 8 detail the IE and clinician dependent measures that will serve as the primary and core secondary outcome measures for the study and the order in which they are to be given.

An IE Manual and a separate Clinician Assessment Manual fully specifies the rationale and procedures for obtaining these dependent measures.

Independent Evaluators

At all full and minor assessment points, an Independent Evaluator (IE) will obtain two primary outcome measures targeting MDD symptoms only: (1) a clinical summary score on the CDRS-R and (2) a CGI-I and a CGI-S.

Table 7: IE Dependent Measures

Measure	Respondent	Assessment Domain
K-SADS	Teenager and Parent	MDD and Comorbidity
CDRS-R	Teenager and Parent**	Continuous measure of MDD
CGI-I	Teenager and Parent*	MDD-specific improvement
CGI-S	Teenager and Parent*	MDD-specific severity of illness
CGAS	Teenager and Parent	Global functioning
HONOSCA	Teenager and Parent*	Global and specific dimensions of functioning

*Record single summary measure by rater using data from both respondents

**Record teenager, parent and rater's summary/combined scores

The CDRS-R will be given first to the patient, then to the parent and then, if necessary, the IE will interview both together to reconcile any differences in reporting before assigning CGI scores.

Relative to baseline status, the CGI-I will be anchored as follows:. 1=very much improved, 2=much improved, 3=minimally improved, 4=no change 5=minimally worse, 6=much worse and 7=very much worse. Relative to normal functioning for an age, race, gender and community matched peer, the CGI-Severity (CGI-S) score will be anchored as follows: 1=normal, not at all ill, 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, 7=among the most extremely ill.

The CGAS[101] will be used to index global functioning at each IE visit. In addition, the IE will complete a HONOSCA to judge domain and global functioning at visit C1, week 12, week 36 and at months 6 and 12.

Clinician Evaluators

Clinician raters (targeting global symptoms/functioning) will independently complete an MDD-specific CGI-I and CGI-S to assess improvement or severity of illness at each office visit. Finally, to judge overall impairment (and by assessing its inverse, improvement) each clinician (1 for CBT and MED and 2 for COMB) will also complete a CGAS [101] targeting overall functioning, including impairments stemming from MDD as well as all other causes, e.g. comorbidity or family problem, combined.

Table 8: Clinician Dependent Measures

Measure	Respondent	When	Assessment Domain
ADS	Teenager	All	MDD, Hypomania and mania
CGI-I	Teenager and Parent*	All	MDD-specific improvement
CGI-S	Teenager and Parent*	All	MDD-specific severity of illness
CGAS	Teenager and Parent*	All	Global functioning

*Record single summary measure by rater using data from both respondents

Procedures

The standard NIMH Clinical Global Impressions Scales (CGI) for severity and improvement (CGI-S, CGI-I) have become standard rating scales across many kinds of studies for both children and adults. They allow the clinician rater or independent evaluator in a clinical trial to establish both the severity of the patient's condition at baseline, and the level of change due to treatment. In a multi-site trial it is especially important that different clinicians have common standards for the use of the CGI Scales, 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 using the CGI Scales are also necessary to ensure that the same rater rating the same patient accurately captures the initial status of the patient and subsequent change with treatment. By reducing unreliability between and within raters, the validity of the trial is protected from method variance in application of CGI Scores. To this end, TADS IE and Clinician Assessment Manuals specify guidelines or algorithms that cover IE and clinical ratings for the CGI scales and, in a linked fashion, all other dependent measures.

7.4. Definition of Improvement and Deterioration

The decision to administer no, maintenance, or additional treatment depends on clinical status at each Stage of treatment, which is why treatment procedures in TADS are consistent with emerging best practice standards for managed care, where a stages of treatment model is *de rigeur*.[39] However, clinical (or IE) definition of severity and improvement is not necessarily the only or even best fashion for examining this question from a data analytic point-of-view. For example, it is also important to ask to what degree treatment "normalized" participants using population normed measures. To examine these issues, we will employ three methods: First, we will use the methods and definitions of Jacobson and Truax,[102] who recommend the use of two reference points for normalization: 1) movement half the distance from participants' baseline scores to some hypothesized normal range; and 2) movement to within 1 standard deviation of the normal range. Using the norms established for the RADS, we will determine whether subjects met neither, one, or both criteria. Second, we will ask whether patients continue to meet DSM-IV criteria for major depression on the K-SADS. Third, we will ask whether patients moved into the normal range on the CDRS-R

7.5. Stage IV Relapse

All patients in Stage IV will be assessed for relapse by the IE at assigned intervals. The criteria for relapse in patients previously judged to be responders is as follows: patient shows a clinician rated CGI-I $\geq$ 4 (no improvement from baseline or worse). Patients will be told that if their MDD symptoms worsen between assessment visits, they should call their primary clinician to schedule an additional visit (within 3 days) for the purpose of clinical assessment. If the patient appears to the clinician to be relapsing (CGI-I $\geq$ 4), then an IE visit should be scheduled and the patient referred for open community treatment according to previous enumerated referral procedures.

7.6. Patient Safety, Adverse Event Reporting and ASAP Procedures

AE reporting and ASAP procedures are defined in detail in the TADS AE/ASAP Manual.

To ensure patient safety and to evaluate the tolerability of treatment, TADS will require careful monitoring of: (1) affective disorder symptoms, (2) adverse events, (3) concomitant medications and (4) out-of-protocol interventions. To this end, this manual has been developed to delineate and standardize procedures for **Adverse Events Monitoring** and **Adjunctive Services and Attrition Prevention** that will be necessary to address those clinical crises and concerns that inevitably will arise in the course of treatment during the NIMH Treatment for Adolescents with Depression Study (TADS). To balance feasibility with our need to gather important information, TADS stays carefully centered between the FDA regulatory approach (record everything) and need to minimize subject and investigator burden.

Definitions

Adverse Event

An adverse event is defined as any unfavorable medical change that occurs during or after beginning the study that may or may not be related to or caused by the study drug or CBT treatment. This includes the following:

1. Any medical event that causes clinically significant interference with functioning (e.g. headache that causes school absence or otherwise restricts activity).

2. Any event that requires medical attention, e.g. a URI with visit to a doctor.

3. Any medical event that induces the subject to take a concomitant medication (e.g., URI that causes the subject to take an over the counter decongestant).

AE reporting does NOT include pre-existing conditions or illnesses that do not worsen or increase in frequency during the study period.

Adverse events may or may not trigger ASAP procedures, with the distinction between those that do and those that don't primarily driven by whether out-of-protocol interventions are required to manage the AE.

Subject-Initiated Protocol Violations

If it is discovered during or after the study that a subject actually received a "cross-treatment" on his/her own (e.g., a parent reveals that an adolescent in the CBT-only group actually received fluoxetine from his or her private physician during the study), we will document the cross-treatment in the clinical record, the concomitant medication log and, for later analysis, the CASA. While TADS staff is expected to discourage treatment outside the study, these subjects would continue to be treated within their assigned treatment arm. Stated differently, subject initiated protocol violations do not trigger AE monitoring unless conditions for AE monitoring are met (e.g. taking an out-of-protocol medication recorded on the CML) or ASAP unless other indications for ASAP are present (e.g. worsening panic inducing the subject to seek unauthorized outside treatment).

Premature Termination

At any time during Stages I, II or III subjects may deteriorate or develop clinical crises that lead the TADS site team to recommend termination from the study treatment (but almost never the assessment) portion of the protocol. For example, a subject who became psychotically depressed, suicidal or manic and required hospitalization would almost by definition require open clinical treatment under emergent ASAP rules. Others will continue in TADS treatments but also will require treatment outside the study as determined under elective ASAP procedures. All such subjects should continue in their assigned arms insofar as possible. For example, medication-only subjects who had been given CBT treatment under ASAP procedures would continue to receive the medication treatment according to protocol, including monthly medication evaluations; CBT-only subjects who had been referred for medication by the treatment team under ASAP procedures would continue to receive as much of the CBT treatment as possible. Such patients will be considered "premature terminators." These are equivalent to "investigator-initiated protocol violators." "Prematurely terminated" subjects may continue to be treated within their assigned treatment arm (as long as this does not pose a danger of contaminating the

treatment of other subjects in that arm) and we would continue to collect assessments throughout the remainder of their scheduled time in the study.

"Drop Outs"

Subjects who terminate prematurely are to be distinguished from "drop outs," defined as subjects who refuse to furnish further data. Stated differently, dropouts are defined as those subjects who withdraw consent from the assessment portion of the study. Subjects who drop out are not eligible for TADS treatment. A subject who drops out should be encouraged to return for a last full (or, failing that, a minor assessment), which would then be followed by end-of-treatment recommendations. If a parent is willing to furnish data, but a subject is not, this subject is not necessarily defined as a "drop out," but all such cases should be reviewed by the ASAP panel.

Affective Disorders Monitoring

At each visit all subjects will complete an Affective Disorders Screen (ADS) that will serve as the basis for review by each clinician (pharmacotherapist in pills only and COMB and CBT therapist in CBT) regarding how the patient is doing with respect to his or her affective illness. The ADS is modeled on the CDRS for MDD and the Young Mania Rating Scale (YMRS) for hypomania and mania. The patient portion of the ADS will use a dichotomous outcome (Symptom present, Yes/No); the clinician will then score on a 0-3 point scale as absent, mild (present, no interference), moderate (present, some interference), severe (present, major interference). This data, which will be transmitted to the CC for scoring, will be used to guide appropriate clinical care. **Either mania or worsening MDD may trigger ASAP; only mania is considered an AE, however.** Further information on the ADS is available in the Clinician Assessment Manual.

Timing of Assessments

At the point of premature termination or "dropping out" an additional full assessment battery will be obtained unless the last full assessment battery had been obtained within the prior month. If the next scheduled full assessment is due within 1 month of this "early termination" assessment, that scheduled full assessment should be skipped. Patients who drop out should be reminded of their obligation to the study and encouraged to complete a last minor assessment battery, or better, a last major assessment battery that would then be followed by end of treatment recommendations.

Forms

As shown in Table 9, TADS uses one patient and three clinician forms to monitor patient safety. The patient form is an Affective Disorders Screen (ADS). The site forms are an Adverse Event Log (AEL), a Concomitant Medication Log (CML) and an ASAP Log (ASAPL).

Table 9: Patient Safety Measures

Domain	Measure	Informant*	Who fills out form?
Affective Disorders	ADS	Patient	Patient / CBT or Pharmacotherapist every visit
Concomitant Medications	CML	Patient	CBT Therapist as needed Pharmacotherapist as needed
Adverse Events	AEL	Patient / Parent	CBT Therapist Pharmacotherapist as needed
Serious Adverse Events	SAE Log	Patient / Parent	Primary Therapist as needed
ASAP	ASAP Log		Primary therapist

*The ADS, AEL and CML are filled out based on patient information, with input from the parent as needed. The SAE and ASAP log require parental input.

Adverse Event Monitoring

Adverse Events

Adverse events will be monitored identically across all treatment arms for the duration of the study.

Specific principles for monitoring affective disorders, adverse events, concomitant medications and their relationship to ASAP are as follows:

Affective disorders will be monitored using the ADS and general clinical inquiry. New onset psychiatric symptoms, such as emerging mania or panic attacks, will be recorded if they cause clinically significant interference with functioning as defined above. Symptoms of major depression will not be recorded on the AEL, but will be tracked on ASAP as required by standard ASAP procedures.

At every visit, the treating clinician (CBT or pharmacotherapist in monotherapy conditions; pharmacotherapist for patients in COMB), will ask about any new health problems that caused the patient to alter his daily routine, seek medical care or take a new medication. The latter includes reviewing the CML, which will have been completed by the study coordinator prior to the visit and reviewed by the clinician. Those events that meet AE criteria (listed above) will be recorded in the AEL.

AE tracking will be by study week of occurrence and remission, not by actual date of onset/offset. An event that occurs more than once per week would be entered once by maximum severity.

Wherever possible, group classification, e.g. the flu rather than headache, fever and cough, will be used in preference to recording individual symptoms.

Not all adverse events, e.g. pneumonia, will initiate an ASAP intervention; not all ASAP interventions, e.g. withdrawal of consent, will occur in response to an AE. However, every event recorded on the AEL will specify whether or not an ASAP procedure was initiated in response to the AE. Every ASAP Log entry will specify whether the ASAP procedure involved an adverse event (recorded on the AEL).

Withdrawal of consent (drop out) or premature termination will be recorded on the ASAP Log, not on the AEL.

Serious Adverse Events

Any serious adverse event or death must be reported immediately to Lilly (if taking medication) and to Duke irrespective of treatment condition regardless of the circumstances or suspected cause if it occurs or comes to the attention of the investigator at any time during the study. Any SAE occurring at any

other time after completion of the study must be promptly reported if a causal relationship to study drug is suspected.

A Serious Adverse Event (SAE), is defined by the FDA/Lilly as:

- Life threatening (at immediate risk of death)
- Requires hospitalization for any reason
- Results in persistent or significant disability or incapacity
- Results in congenital anomaly or birth defect
- Results in death
- Other significant medical event including cancer.

The only exception to the above reporting requirement is SAEs occurring during the screening phase prior to randomization.

Concomitant Medications

Per the functional definition of an AE, which includes taking a concomitant medication, the treating clinician (pharmacotherapist in all pill conditions or the CBT therapist in CBT) will review the CML, which will be completed by the study coordinator. The CML will include the name of drug, self-medication or doctor Rx, and week of starting and stopping drug will be recorded on the Concomitant Medication Log (CML).

As appropriate, concomitant medications, whether over-the-counter (including herbal medicines) or doctor's Rx, will be linked to the AEL in the following fashion: the proximate cause of taking the medication will be the AE recorded on the AEL.

In case of an out-of-protocol medication for a psychiatric indication (e.g. hypericum), the AE will also trigger ASAP if and only if the primary clinician/site team believes that ASAP is warranted.

Physical Symptom Checklist

Patients will complete a self-report Physical Symptom Checklist (PSC) at baseline and at every assessment point throughout the trial. The PSC will use present/absent anytime in the past week. This data will **not** be used to guide clinical treatment or to trigger AE or ASAP reporting or action, but will be useful in documenting the extent and nature of physical symptoms within and between treatment groups across time.

ASAP

Types and indications for ASAP are as discussed below. The reason for ASAP referral, the decision of the ASAP Panel and the outcome of the ASAP intervention will be recorded on the ASAP Log. For each AE, the clinician will note on the AEL whether that AE triggered ASAP. If the answer is yes, then the ASAP Log should be completed.

Consistency of Records

It is the task of the study coordinator to review the AE, SAE, CML and ASAP records to make sure that they are consistent in "real time" so that clinical care of the patient does not suffer from lack of attention to AE/ASAP monitoring. At the point of data entry, the CC will also "flag" inconsistent records using standardized edit rules to generate queries to the site.

Overview of Adjunctive Services and Attrition Prevention (ASAP)

It is expected that most subjects will exit TADS treatments at Stage I (clinician-defined non-responders and PBO subjects) and at Stage III (completers). However, some patients may withdraw consent for both treatment and assessment (**drop out**) and others may suffer sufficient clinical deterioration from whatever source that the treatment team recommends that continuing TADS treatment is no longer appropriate or that additional out-of-protocol treatment is required (**premature termination**). Other patients/families may require out-of-protocol interventions during study entry or during Stage IV. To meet these needs for out of protocol treatment, two ASAP sessions will be available during screening, four during Stages I and II, four during Stage III and two during Stage IV. A single ASAP session not from the "bank" of ASAP sessions noted above may be used to manage dropping out. Finally, family members may require treatment outside the study. **To guarantee cross-site consistency and excellent clinical care for TADS patients, these situations will be managed via ASAP procedures as specified in the ASAP manual.**

As presented in detail below, there are 8 ASAP codes (settings requiring ASAP) each coupled to a specific set of allowable interventions. These involve ASAP during entry procedures, emergent and non-emergent clinical situations, ASAP during Stage IV, dropping out, and referral of family members for treatment outside TADS.

ASAP 1: ASAP During Entry

During the Gate B to C entry period, two ASAP sessions will be provided. Subjects in crisis at Gate A or between Gates A and B will be referred to community resources as appropriate. To avoid biasing post-randomization treatment, these ASAP sessions will involve assessment and supportive counseling without specific behavioral programming or treatment recommendations.

ASAP Indications 2, 3, 4, 5 During Stages I, II and III

It is expected that most subjects will exit TADS treatments at Stage I (IE defined non-responders and PBO subjects) and at Stage III (completers). If necessary, however, ASAP provides consistent procedures for addressing two situations that may threaten a subject's full participation in TADS:

- Emergent (site acts before ASAP Panel review) and non-emergent (site requests ASAP intervention) clinical situations affecting the welfare of the adolescent and his/her family.
- Situations potentially leading to premature termination.

Crossing these two exigencies, clinical emergencies and possible premature termination, generates the four situations detailed in Table 10 that define the domain of ASAP during TADS Stages I, II and III.

Table 10: ASAP During Stages I, II and III

	Premature termination No	Premature termination Yes
Clinical Emergency No	ASAP 2: Non-emergent situation not leading to premature termination	ASAP 3: Non-emergent situation leading to premature termination
Clinical Emergency Yes	ASAP 4: Emergency not leading to premature termination	ASAP 5: Emergency leading to premature termination

ASAP 2: At any time during Stages I, II or III, non-emergent clinical situations may develop that lead the TADS site team to recommend brief out-of-protocol interventions that do not lead to termination from the treatment or assessment portions of the portion of the protocol. For example, if family conflict interfered with a medication subject's willingness to complete an assessment point, the family could receive one or two family sessions from the study team under ASAP rules. If the situation did not resolve with a brief ASAP intervention because family conflict proved an enduring problem so that further treatment outside the protocol was required, then ASAP 2 applies.

ASAP 3: Other subjects will continue in TADS treatments but also will require elective treatment outside the study because of ongoing clinical situations that cannot be met within the framework of their TADS-assigned treatment or by using brief ASAP interventions. Such patients will be considered **"premature terminators"** and are equivalent to "investigator-initiated protocol violators." All such subjects continue in their assigned arms insofar as possible, e.g., prematurely terminated subjects may continue to be treated within their assigned treatment arm (as long as this does not pose a danger of contaminating the treatment of other subjects in that arm) and we would continue to collect assessments throughout the remainder of their scheduled time in the study. For example, medication-only subjects who had been recommended by the ASAP Panel for CBT treatment would continue to receive the medication treatment according to protocol; CBT-only subjects who had been referred for medication by the treatment team under ASAP procedures would continue to receive as much of the CBT treatment as possible.

ASAP 4: Analogous to ASAP 1 but more emergent, some subjects will develop clinical situations that require immediate intervention without waiting for ASAP Panel approval. For example, a subject who developed acute school refusal because of panic attacks could receive brief clinical treatment from the study team under ASAP rules. If the crisis does not resolve and further treatment outside the protocol is required, then ASAP 2 applies.

ASAP 5: At any time during Stages I, II or III, subjects may develop clinical emergencies that lead the TADS site team to recommend emergent termination from the treatment (and sometimes the assessment) portion of the protocol. For example, a subject who became psychotically depressed, suicidal or manic and required hospitalization would almost by definition require open clinical treatment under emergent ASAP rules.

ASAP 6: ASAP During Stage IV

In Stage IV, two ASAP sessions will be provided for the purpose of crisis assessment and referral to appropriate community providers. No treatment will be provided during these sessions. However, to meet our ethical responsibilities to TADS patients and to assist with "sample maintenance," appropriate crisis/case management should be provided as clinically appropriate outside the study.

ASAP 7: Dropouts

Some subjects may refuse participation (withdraw consent) from the treatment but not the assessment portion of the study. Such subject should be encouraged to continue in treatment, but ASAP procedures are not invoked as this situation should be managed by the teen's primary clinician within the framework of the assigned treatment using ASAP procedures as indicated above.

Conversely, subjects who refuse participation in the assessment portion of the study are considered **"drop outs."** Subjects who drop out are not eligible for TADS treatment.

A single ASAP session in addition to the bank of ASAP sessions outlined above may be used to address the reasons why a family/patient may withdraw consent from the assessment portion of the study and to try to persuade, if possible, the family/patient to continue their participation. At a minimum, the parent or teenager should be encouraged to complete the major assessments even if the other will not do so, including a major assessment point at the point of dropping out.

ASAP 8: Referral of Family Members

Circumstances may arise during TADS where it is apparent to the TADS treating clinicians that a family member residing in the home with the TADS teenager requires referral for mental health services. While TADS team members should not take on the responsibility for treating family members other than the TADS subject, it is important for ethical and pragmatic reasons to refer family members to treatment appropriately. For example, maternal depression has been identified as a significant predictor of poor outcome in the treatment of pediatric MDD and should prompt referral (if possible) for clinical services outside TADS. Such a referral should be considered when the baseline BDI for either parent is > 20 and at any other point in the study when referral appears indicated on clinical grounds. Note that in no instance should referral for treatment include treatment that overlaps TADS treatment, e.g. a referral for behavioral family therapy unless the recommendation is made in the context of ASAP indications 2-5.

8.0 Data Management

8.1. Overview

TADS will generate numerous data collection and tracking forms per subject over the course of the recruitment and 36 week treatment and 52 week F/U periods. DCRI will provide centralized data management services for data collected. Measures across the domains of psychopathology, internalizing and externalizing symptoms, social interaction and functioning, peer relations, academic and school performance, family processes and interaction, parenting, medication, and side effects will be completed at various assessment points throughout the study. Considering that there will be 432 subjects or more (48 or more subjects per each of 9 sites), it is clear that a well-organized, well-regulated system of data collection, entry, management, transmittal and editing is essential.

A critical component is the development of a data management plan that documents key processes and procedures. The plan is incorporated in a project specific data management binder that includes the protocol, scope of work, annotated data forms, database structure, query rules, data flow scheme, Trial Specific Work Instructions (supportive details to the DCRI Standard Operating Procedures) for all Data Management processes, copies of supporting forms and data clarification forms, test plans and audit plans. The data management binder is developed and maintained by the Clinical Data Specialist (CDS), is updated to reflect the current status of the study, audited prior to production work on the trial being performed, and audited at planned Data Management Quality Control audits.

8.1.1. Database Development:

The DCRI will develop and support data entry, tracking and query systems for the study. The database development environment used at DCRI is ClinTrial (version 4.1). All development within ClinTrial and all additional programming performed in development of the database are validated according to a predetermined plan. Key components of this activity include data entry screen programming and

database testing and validation.

8.1.2. Data Coding/Entry/Verification/Tracking:

Adverse events, concomitant medications, non-drug treatments and medical history are encoded using standard dictionaries (i.e. MedDra, WHO DRUG, COSTART, ICD9CM). Code assignments for terms that fail autoencoding are completed after clinical review.

Assessment and treatment data forms are mailed to the DCRI after each assessment is completed. The forms received are checked for completeness and compared to the assessment checklist. These forms are processed according to trial specific requirements. All data from these forms are entered into a study database. The ID of the data entry person (e.g., two-letter initials) and the date of entry (an automatic, derived variable) are included on each record to aid tracking. Quality-control checks are performed, and discrepancies, identified at entry and double entry, are flagged for resolution through the formal discrepancy-management system.

Key component activities include:

- Receipt and tracking of physical data forms
- Secure storage of physical data
- First and second entry of data
- Coding of entered data (e.g., adverse events, concomitant medications)
- Transfer of data to sponsor at conclusion of trial.

8.1.3. Data Validation

The primary validation of data occurs in the ClinTrial database. Data-quality procedures include checks for completeness, real-world values, logical inconsistencies, compliance, safety irregularities, and fraud. Electronic data validation checks are developed using data entry discrepancy flags, programmed rules within ClinTrial and, in certain cases, external rules using PL/SQL or SAS code. The query rules that are used to define range and limit checks for individual variables and to check for consistency among a combination of variables are specified based on past experience with similar types of data.

Key components of this activity include:

- Preparation of query rule specifications
- Data validation check programming
- Specification of test plan, entry, and review of test data
- Review discrepancy reports from validation test
- Preparation of data clarification forms for sites
- Review and reconciliation of data clarification forms

8.1.4. Database Quality Control

The Data Management function at DCRI has four levels of quality control. The first level of database quality control is our double entry process. The second level of quality control consists of programmatic range and consistency checks. These checks are specified in a document called the query rules. The programmatic checks are run nightly on data that has been through the double entry process. The third level of database quality is a record or panel level of control. Our Quality Control and Reporting group within Clinical Data Integration maintains programs that identify suspected duplicate and blank or missing records and records not double entered within and across database tables. These programs are run on a weekly basis (or can be executed on demand) for all trials. An independent auditing group within Clinical Data Integration performs the fourth level of database quality control. These internal data quality and process compliance audits are routinely conducted on all ongoing studies to document the frequency of random errors and identify systematic deviations so that they can be corrected. An audit is usually performed at 3 timepoints, 10, 50 and 100% of data in house.

8.2. Web Site

The Web Site will be used to report information back to the sites -(e.g., study and site activity reports, number of patients screened and/or enrolled at each site). The project Web site will be located on a SSL (secure socket layer, 128 bit encryption web server) and will be username and password protected. An additional site level will exist within the Web site that will contain specific site appropriate files and reports viewable only by the appropriate site and the CC.

8.3. Subject Randomization to Group Assignment

As stated above, subjects who meet all study eligibility criteria and who sign Informed Consent will be randomized to one of the four arms after the completion of their Baseline Assessment. Randomization is done after assessment to help ensure that Baseline Assessment data will be obtained without knowledge of treatment assignment by either the subject or rater. Also, this will help to ensure that Baseline Assessment data are obtained equally for all treatment arms in case of differential cooperation after random assignment.

Treatment assignment will be obtained by calling the Coordinating Center randomization service.

The subject will keep the same subject number upon randomization to treatment assignment. The computerized randomization algorithm will "choose" the assignment for the subject and automatically insert the group assignment into a "group assignment" variable in the data system. Since group assignment is not blind (other than MED and pill PBO), the computer will also produce paper output with this assignment to help ensure that it is implemented accurately.

Patients randomized to FLX, PBO or COMB will be assigned a study drug kit number by the randomization service at DCRI. The kit number is linked to the treatment condition within the randomization database system. To ensure blinding of the pill conditions (pill PBO and FLX), the site will only be informed of the study kit number assigned to the patient.

8.4. Data Access During TADS

Overview

Statistical analysis of baseline measures will commence once the entire sample has been recruited. With the exception of embedded psychometric and quality assurance analyses, statistical analysis of treatment outcome will not be conducted until the final subjects have completed the trial.

Exceptions

To protect the blind, only the TADS Statistical Team (Dr. Silva and her colleagues) will have access to the data analysis datasets and findings that pertain to the DSMB reports. Adverse Events data, however, will be available to the TADS Team. With the exceptions noted below, no access will be granted to baseline or after-baseline data other than measures specifically intended for ongoing clinical treatment monitoring according to the various treatment protocols.

- Summary measures will be made available to the psychotherapist and/or pharmacotherapist as part of the Orientation Visit.
- Baseline and the most recent full assessment visit will be made available to the site team for the purpose of generating end-of-treatment recommendations.
- The clinician (CBT and pharmacotherapist) will have access to the ADS, CGI-S, CGI-I and CGAS scores in tabular or graphical form beginning with the baseline data.
- The Independent Evaluator (IE) will have access to the baseline and most recent CGI-S and CDRS ratings and, when conducting the K-SADS, the baseline and most recent K-SADS elements that are current set for ascertainment. These will be provided as the original notes and in tabular and, where appropriate, in graphical format.

9.0 Data Analysis

The Coordinating Center (CC) will perform statistical analyses as required by NIMH and prepare periodic reports for presentation to the Steering Committee, the Scientific Advisory Group, and the Data Safety and Monitoring Board (DSMB). The CC will make every effort to address the scientific questions of the study with quantitative findings. Reports will include descriptive information for monitoring study progress and statistical analyses that are relevant to both primary and secondary hypotheses. The CC will participate in the preparation of scientific papers for publications and presentations based on the study data. The CC will work closely with NIMH and the clinical sites in developing both descriptive summaries and detailed statistical analyses plans. Routine reports will be computer generated once the formats for these reports are finalized.

9.1. Descriptive Analyses

Monitoring the Study. The CC will summarize for each phase by site and overall the general status of enrollment, data collection and study quality. Enrollment information will include the status of recruitment relative to recruitment goals, a descriptive characterization of the screened and enrolled subjects (e.g., age, gender, ethnicity, SES, IQ, entry criteria, baseline rating scores, comorbid disorders, parent symptoms), and the tracking of patients through various paths from presentation at the sites to eligibility for different phases that constitute the protocol. Data collection will be depicted in terms of forms received, delinquent data, edit failures, study withdrawals and losses-to-follow-up.

Outcomes. The study design includes several observational segments (e.g., Stage I treatment study, Stage II-III maintenance and extension, and Stage IV open follow-up). Point estimates and confidence intervals will be provided for means and proportions to quantify results from these segments.

9.2. Detailed Analyses

9.2.1. Intent-to-Treat Approach

Data from all randomized patients will be included in the group to which random assignment is made. Thus, analysis will be by intention-to-treat regardless of later events. Additional approaches to the analysis may be provided for support or explanation, such as analysis for participants that complete treatment as planned. Losses-to-follow-up present problems of interpretation with any approach. A loss-to-follow-up may be labeled as a nonresponse for a dichotomous outcome. The last observation carried forward may also be used for measurements at a specific time point, irrespective of the duration of

treatment. The characteristics of patients that are lost-to-follow-up will be compared with those that remain on study.

Categorical Outcomes

For a dichotomous outcome (e.g., response versus nonresponse), Pearson's chi-square statistic will be used to evaluate overall treatment differences. There will be a number of covariates to consider in the analysis. One of these covariates, clinical site, is a component of the randomization design. Other covariates are of interest as they pertain to the external validity or generalizability of the study, such as age, gender, and ethnicity. Thus, the Mantel-Haenszel statistic will be used to test for overall treatment differences on a dichotomous response controlling for site; and logistic regression models will be used, in general, to quantify the effects of covariates on outcome while controlling for other variables in the model. These three analysis methods are easily implemented using SAS.[103] PROC FREQ provides the nonparametric randomization-based methods (Pearson's chi-square and Mantel-Haenszel statistic) and PROC LOGISTIC can be used for modeling. StatXact[104] may be needed to determine the p-value for the Mantel-Haenszel statistic if sample sizes within clinical site are too small to justify approximation with the chi-square distribution.

For categorical outcomes with more than two categories, there are corresponding methods to those noted above for the dichotomous case. Koch and Edwards have summarized some useful methods.[105] In the proposed study, a notable example is the 7-point Clinical Global Impressions Scale (CGI). This outcome is ordered categorical. A nonparametric, randomization-based statistic will be constructed to account for the ordering via a set of scores (e.g., integer) reflecting response levels. This statistic is useful for detecting a location shift across the ordinal response between treatment groups. An extension of the Mantel-Haenszel method will be used to control for site. Finally, the proportional odds model extension of logistic regression will be used to consider covariates. Again, the methods can be implemented using SAS[103] with PROC FREQ and PROC LOGISTIC.

9.2.2. Time-to-Event Analysis

Time-to-relapse over a follow-up period of 12 months is the primary outcome for Stage IV. Kaplan-Meier[106] methods and Cox regression[107,108] will be used to analyze the interval of time from randomization to relapse. Kaplan-Meier curves provide estimates of the failure-time distribution from the observed data (for example, the cumulative proportion of patients that relapse by time *t*) with no parametric assumptions. These curves will be presented routinely for visual comparison of the treatment groups. A corresponding log-rank statistic will be provided to assess differences in the curves; and a stratified log-rank statistic will be provided to assess treatment differences while accommodating heterogeneity across clinical sites. Control for additional covariates and the evaluation of the effects of covariates on outcomes will be handled using Cox regression. This is a semi-parametric method that requires the assumption of proportional hazards without further specification of the hazard functions. SAS[103] provides procedures that can be used to do these analyses: PROC LIFETEST for the Kaplan-Meier and log-rank statistics and PROC PHREG for Cox regression models.

Continuous Outcomes

Some of the secondary outcomes that have been noted for the study are continuous in nature. These outcomes include depression rating scores and various measurements of functioning. The Kruskal-Wallis test for J independent samples (e.g., 2 or 4 treatment arms) will be used as a nonparametric method to assess treatment differences in addition to ordinary regression methods. Although the study will be randomized and we do not expect imbalances in baseline prognostic variables, we will guard against such imbalances as well as possibly provide some reduction in the error variance by including baseline values of the outcome variables as covariates in the regression models. Thus, the linear models will include treatment, clinical site, and the baseline prognostic variable. We will make the usual checks of assumptions in the regression analysis including normality of the data and homogeneity of variance. If the data are nonnormal or the variances heterogeneous, we will transform the data to achieve better compliance with the assumptions. These methods can be implemented using SAS.[103] PROC

NPAR1WAY provides the Kruskal-Wallis test and PROC GLM can be used for linear models. In addition, PROC REG performs linear regression with many diagnostic capabilities. Finally, as noted earlier and again immediately below, we will use multi-level models wherever appropriate as implemented in PROC MIXED or specialized program, such as HLM4 or MLWin.

Interactions

For any type of outcome— categorical, time-to-event, or continuous—it will be important to assess the homogeneity of effects across various subgroups. The assessment for interaction of a covariate with treatment or another covariate will be through the corresponding parametric model for the outcome. Consideration of interactions will be necessary for evaluation of goodness-of-fit of the model as well as to strengthen the conclusions of the study with respect to generalizability. Several covariates have been mentioned. These include clinical site, age, gender and ethnicity.

9.2.3. Longitudinal Data

For all phases, there will be repeated measurements on several outcomes of interest. Primary analyses may focus on outcomes at particular time points. However, analysis of the repeated measurements make it possible to study the time course of effects, use all of the data, and may produce more efficient estimates. Analyses of repeated measures data need to accommodate the statistical dependence among the repeated observations within subjects as well as the type of outcome. The repeated measurements that have been proposed are both categorical and continuous.

Most of the methods that are available for repeated measurements can be grouped into two classes: a subject-specific approach via a random-effects model; and a population-averaged approach via the generalized estimating equations (GEE) method.[109] For normally distributed data, the random-effects model of Laird and Ware[110] is widely used. SAS provides this method in PROC MIXED.[111] For generalized linear models, a penalized quasi-likelihood approach to random-effects was proposed by Schall[112] and Breslow and Clayton.[113] This method is implemented by iteratively fitting a linear mixed model to a modified dependent variable. The SAS macro GLIMMIX[114] provides access to this method. SAS[111] has recently added the GEE method to PROC GENMOD.

Longitudinal data analysis will be included in the evaluation of treatment effects for the proposed study. The particular approach will be determined during planning.

9.2.4. Evaluating Potential Mediating Factors

Freedman, Graubard, and Schatzkin[115] discuss an operational criterion for the statistical validation of an intermediate endpoint for a chronic disease. The test involves determining whether a treatment effect, adjusted for the intermediate outcome, is reduced to zero. An example is given of the cholesterol lowering drug cholestyramine for coronary heart disease with the intermediate outcome being serum cholesterol levels. The analysis is akin to causal modeling and has been presented in that context by Susser.[116] This approach may be useful in understanding primary results, treating, say, compliance as an intermediate variable. The method will permit evaluation of compliance and other potential mediators as explanatory of some important proportion of the treatment effect.

9.3. Cost and Cost-Effectiveness Analysis

Our approach to cost and cost-effectiveness analysis follows the approach described by Gold et al.[117] The first step in cost-effectiveness analysis is to estimate the expected costs of each treatment regimen. Using the clinical outcome probabilities (from the main findings of the clinical study), we will calculate the expected cost of each therapy (FLX, CBT, and COMB) by multiplying the probability of each clinical outcome and the associated costs of that outcome and summing these products over all the clinical outcomes.

Our cost-effectiveness analysis will first estimate the cost-effectiveness of each of the treatments relative to PBO. This will provide information on whether each of the interventions is cost-effective relative to no treatment. The cost effectiveness analysis will involve computing the ratio of the

difference in cost of each of the treatments (relative to PBO) to the difference in effectiveness (relative to PBO). The main effectiveness measure in the study is the CGI score. These cost-effectiveness ratios will be compared to determine which of the treatments is the most cost-effective intervention (relative to PBO). In addition, these ratios can be compared to other cost-effectiveness ratios for other anti-depression interventions (from the literature) that use the CGI or PQ-LES-Q scores as the effectiveness measure to assess which intervention is the most cost-effective.

Second, we will assess the cost-effectiveness of combination therapy relative to FLX and combination therapy relative to CBT by computing incremental cost-effectiveness ratios. These two ratios are defined as the ratio of the difference in costs between COMB and FLX (CBT) to the difference in effectiveness between COMB and FLX(CBT). These ratios will inform us at to whether it is more cost-effective to adopt combination therapy relative to FLX or CBT.

Although Gold[117] recommends the use of quality-adjusted life years (QALYs) as the effectiveness measure, we propose to use the CGI and score as the primary effectiveness measure and the PQ-LES-Q (PQLQ) as a secondary measure. Because the maximum time that patients are followed in the study is only 72 weeks, the period is too short to capture any meaningful differences in QALYs. Significant differences in QALYs would arise if we developed a Markovian state-transition model to estimate the lifetime costs of treatment for depression.[118] But the development of such a model is beyond the scope of the current project unless the proposed competing continuation allows long-term treatment of the sample into adulthood.

Finally, to confirm that our cost-effectiveness results are robust to changes in assumptions and to examine the stability of the results to key variables, we will perform a sensitivity analysis. We will first perform a one-way sensitivity analysis in which one variable at a time is varied, holding all other variables constant. We will also estimate confidence intervals for our cost-effectiveness ratios. Following Doubilet, et al.,[119] we will use Monte Carlo simulation to generate these confidence intervals as in our previous work.[120,121] Computing the confidence interval around the cost-effectiveness ratios will allow us to account for uncertainty around our variable estimates.

9.4. Preparation for Scientific Meetings and Manuscripts

CC staff will provide assistance and coordination in the preparation of data for scientific conference presentations (e.g., the American Academy of Child and Adolescent Psychiatry), abstracts, and manuscripts for peer-reviewed journals. These will include efforts led by the site investigators as well as studies led by CC staff (e.g., Drs. March and Curry).

Coordination of the analytic and other efforts by the CC is necessary to prioritize and ensure adequate support as well as avoid duplication of effort. A schedule will be set up and guidelines written by the Publications Committee. Statistical Leadership will be provided by Dr. Susan Silva (DCRI Statistical PI) and Dr. Gary Koch (Statistical Consultation). Dr. Silva will assume administrative responsibility for the data preparation and analytical procedures conducted at the Coordinating Center. Statistical staff will also be available to run the analysis needed for the various presentations and manuscripts.

The proposed CC staff fully expects to present results from studies at scientific meetings alongside their colleagues from the sites and NIMH. They also expect to be authors and co-authors of abstracts and manuscripts describing results from the studies. The proposed staff is well aware that the success of TADS, in the eyes of the scientific community, will be measured in terms of publications and presentations rather than more subtle study accomplishments.

The status and progress of the presentations and publications will be tracked electronically and presented to the Scientific Advisory Group and the DSMB, and hard copy materials will be maintained in the study library.

9.5. Final Statistical Reports of Protocol Outcomes

Throughout the data collection phase, we shall prepare interim statistical reports of protocol outcomes that are tailored for the GPO, the Scientific Advisory Board, and DSMB. We will revise our

presentations as needed and directed by the GPO to address concerns raised by these groups during the trial. At least one month before the end of the contract, we shall submit drafts of the final statistical report to the GPO and the contracting officer. It will include outcome analyses from the final database in a format that incorporates suggestions received from the GPO, DSMB, and Advisory Committee throughout the study. We will expect to receive comments on this report from the GPO within 1 week. Before the end of the contract, we will revise the report and submit copies to the GPO.

10.0 Organization, Personnel and Training

The study is designed to be carried out as a contract to the Coordinating Center at DUMC, collaborating staff at the National Institute of Mental Health and investigators at 9 study centers.

10.1. Coordinating Center (CC) Staff

The CC consists of a team of investigators that is experienced at conducting efficacy and effectiveness trials in psychotherapy and psychopharmacology; participating in and coordinating multi-site clinical trials in children, adolescents and adults; and in data management and analysis. Research scientists comprising the team have their primary academic appointments in the Department of Psychiatry at Duke University Medical Center (DUMC) and the Duke Clinical Research Institute (DCRI), with the PI (Dr. John March) having appointments in both settings. DUMC is the prime contractor for the Coordinating Center with the Department of Psychiatry assuming overall responsibility and leadership for the scientific integrity of the study, including coordinating the development of a final study design, site recruitment and selection, and coordination of Steering Committee activities. Within DUMC, the DCRI provides expertise in clinical trials randomization, serious adverse event reporting, site management and monitoring, pharmaceutical expertise and drug supply. DCRI also is responsible for multi-site data management, data processing and assistance with statistical analysis. In relying on the collective experience of the TADS team, the Coordinating Center seamlessly draws on faculty and staff who have a depth of experience in coordinating multicenter trials; supplying drugs for large studies; developing, manualizing and assessing the fidelity of CBT interventions in adult and pediatric mental disorders; and preparing materials for randomly controlled trials.

10.2. Collaborating Research Centers

Site*	PI	Co-PI
1. NYU Medical Center New York, NY	Anne Marie Albano, PhD	Glenn Hirsch, MD
2. Wayne State University Detroit, MI	Nili Benazon, PhD	Marla Bartoi, PhD David Rosenberg, MD
3. Behavioral Health Center Charlotte, NC	Charles Casat, MD	Jeanette Kolker, PhD
4. UT Southwestern Medical Center of Dallas Dallas, TX	Graham Emslie, MD	Betsy Kennard, PsyD
5. University of Nebraska Medical Center Omaha, NE	Christopher Kratochvil, MD	Randy LaGrone,PhD
6. University of Chicago Chicago, IL	Mark Reinecke, PhD	Bennett Leventhal, MD
7. University of Oregon Eugene, OR	Paul Rohde, PhD	Anne Simons, PhD
8. Johns Hopkins Hospital Baltimore, MD	John Walkup, MD	Golda Ginsburg, PhD
9. Children's Hospital of Pennsylvania Philadelphia, PA	Elizabeth Weller, MD	Norah Feeny, PhD Owen Hagino, MD
10. New York State Psychiatric Institute New York, NY	Bruce Waslick, MD	Michael Sweeney, PhD

*NYU and Columbia are a joint site.

Based upon the power analysis and determination of the necessary sample size for the study, 9 centers are included, with NYU and Columbia participating as a joint site, each expected to generate 48 or more patients. Subcontracts to these centers are for 6 years; the first year is devoted to, hiring of staff, finalizing the decisions and procedures to ensure uniformity across sites, implementing the feasibility study in terms of data collection instruments and database management systems, and training of staff in study procedures as well as delivery of treatment and measurement of outcome. Years 2-5 will be devoted to recruiting subjects and implementing treatment and follow-up procedures in Stages I-IV of TADS. It is anticipated that methods and papers focused on analyzing the baseline data also will be completed during this time period. The latter portion of year 6 will be devoted to data analysis and manuscript preparation focused on the study outcome.

10.3. Staffing at Each Site

Overview

At each site, the PI will designate one or two doctoral-level co-investigators who will be members of the TADS Steering Committee from that site and will appear on the TADS "boilerplate" for publication purposes. Of the three potential senior staff, one must be an MD responsible for Pharmacotherapy supervision; one must be a PhD or MD responsible for CBT supervision. The third slot is a swing position, e.g. can be either a PhD or an MD at the PI's discretion and may or may not be the site coordinator. The PI or one of the Co-I will also be the IE supervisor.

Team Meeting

Each site is expected to convene a **weekly TADS team meeting** at which (1) all patients at Gates B and C and Stages I-IV are discussed by their respective therapists in sequence; (2) a decision is made about increasing the FLX dose in patients in COMB with a pharmacotherapist assigned CGI-S score of 3, with input from the CBT therapist; (3) decisions that require site votes on the conference calls are jointly considered; and (4), ASAP interventions are discussed and evaluated with respect to their implementation and intended effects. All site personnel except the IE are expected to attend. Since the IE is participating in pre-randomization assessments, he/she may only be present for the discussion of study eligible (Gates A, B, C) but not yet randomized patients.

Principal Investigator

Responsible for on-site administration, adherence to study design; represents site in collaboration among centers and the NIMH; participates in difficult clinical decisions about individual subjects; represents site to community for purposes of recruitment.

Study Coordinator

Understands all aspects of all arms of the protocol. Responsible for ensuring day-to-day operation of the study. Holds weekly meetings with all site study staff and establishes a subject review format so that all staff are aware of ongoing patient status. Oversees Recruitment and Screening process and assures that eligibility are met at each point (Gate A Telephone Screening, arranges and oversees Gate B intake visit, Gate B2 clinical interview visit, and coordinates Gate C Baseline Assessment); obtains random assignment; ensures that individual subject schedules are set up and that procedures for assessments run smoothly; establishes and oversees procedures for flow of paper data forms and transmission of data to Coordinating Center; maintains close contact with Coordinating Center; maintains close contact with other project staff. Serves as supervisor to research assistants and data entry personnel .

CBT Therapist

Responsible for coordinating and performing all components of CBT treatment subjects assigned to CBT-only (12 subjects) and combined (12 subjects) arms. Ensures that notification is sent to parents of individual parent sessions. Understands all aspects of CBT treatments. Ph.D.-level or equivalent or specially approved.

Pharmacotherapist

Prescribes medication; sees subjects in medication-only and combined groups; does physical examinations; may do case management for medication-only group; may be a member of the Cross-Site Pharmacology Panel; makes recommendations for changes in doses or drugs during the maintenance stage. May be responsible for drug accountability.

Independent Evaluator

Performs Gate B and C K-SADS and CDRS and other pre-randomization assessment measures. Administers IE assessment battery to all patients at designated intervals throughout treatment. The IE is blind to treatment status of patients; must reach same level of proficiency for interrater agreement as other trained staff and be re-certified annually.

Research Assistant

Mailing packets and other correspondence with families, physicians, schools, etc.; appointment setting and follow-up; witnessing consents and assents; administering various computer-based tasks during assessment visits; administering (reading) rating scales to children and recording the responses during clinic assessment visits; logging in receipt of data forms; reviewing paper forms for completeness; tracking down missing forms and items from clinicians, parents, and teachers; accessing computer to

run algorithms and reports to be reviewed by Site Coordinator and Principal Investigator. Aids family members and children during Gate C intake visit.

10.4. Qualifications

Because TADS is an effectiveness study, it is unreasonable and undesirable to assume edge-of-the literature expertise for all the treating clinicians providing TADS treatments. On the other hand, minimum qualifications were necessary to insure a fair test of each of the treatments against pill PBO and against each other. Based on extensive discussion between the CC and the sites, qualifications for CBT therapists, pharmacotherapists and the IE were developed.

CBT Therapist Qualifications

1. Terminal degree plus completion of profession-specific training (residency, internship, or field work for M.D., Ph.D., or M.S.W., respectively).
2. At least one year of clinical experience following completion of #1.
3. At least one year of experience (during or after training) as a CBT therapist.
4. At least two years of experience (during and/or after training) treating adolescents (not necessarily with CBT), including at least 5 adolescents with major depression, with or without comorbid disorders.
5. Commitment to a CBT approach, and willingness to follow a "manualized" treatment, to have sessions audiotaped and reviewed by site supervisor and coordinating center.
6. If a site supervisor wishes to propose a therapist who does not meet all of these qualifications, but has equivalent background and experience, that proposal will be reviewed by a committee consisting of the two coordinating center CBT therapists (Curry and Wells), and one site CBT supervisor other than the supervisor who makes the proposal.

Pharmacotherapist Qualifications

1. An MD, PA or RNP licensed to practice by the state in which the site resides.
2. At least one post-residency year of experience.
3. At least one year of working predominately with children and adolescents.
4. Experience in the pharmacotherapy of adult or pediatric depressive disorders.

These criteria are to a large extent analogous to those instantiated for the CBT arm of the study and insure a fair test of the relative benefits of the treatments alone and in combination.

Independent Evaluators Qualifications

1. MD psychiatrist with experience administering research-related structured clinical interviews
2. Ph.D. or Psy.D. clinical psychologist with experience administering research-related structured clinical interviews
3. DSW or MSW social worker with experience administering research-related structured clinical interviews
4. Psychiatric nurse practitioner with at least 6 months of recent experience administering research-related structured clinical interviews
5. Masters-level psychologist with at least 6 months of recent experience administering research-related structured clinical interviews
6. In addition, all IEs must have experience in making determinations related to differential diagnosis. Experience with research-related structured clinical interviews should preferably be with instruments that assess multiple diagnoses, not just one diagnosis of interest in one study;

7. All IEs must be experienced with depression or with adolescent psychiatric patients or, preferably, both.
8. All IEs must agree to be available for at least 20 months when assigned a new patient.

11. Protection of Human Subjects

This study follows procedures for minimizing risks and ensuring the safety and confidentiality of human subjects, both as established under the Department of Health and Human Services and the Office of Protection of Research Risks. A common consent form describing all aspects of the study will be adapted at each site to meet the requirements of each local IRB. The nature of all possible treatment assignments as well as their risks and potential benefits will be fully explained to both children and their families. Each site will take appropriate measures to ensure the confidentiality of the data as well as the well being of their subjects.

11.1. Recruitment and Consent Procedures

Overview

The recruitment procedures for TADS must include a thorough explanation of the study, time commitment, possible risks and benefits, and about the alternatives for treatment.

Parent Consent

Participants will be informed about the purposes of the research study. Specifically, they will be informed about the diagnosis of MDD and its treatment. Through a combination of written materials and the consent form, they will be told that this is a treatment study, and each of the four study arms will be described, including details of each of the treatment components. They will be informed that they have an equal chance (random assignment) to be assigned to any of the four study arms. Details of the Stage II-III treatment maintenance/extension protocol will be explained, as will the differences between early termination and dropping out and the consequences of each. The Stage IV follow-up will be described, including procedures for managing relapse. They will be further informed that their family's and teenager's identity will be kept confidential, through the use of a confidential code number which will allow all information to be entered into the database in an anonymous fashion, such that information cannot be linked or traceable to any person or family. Aside from treatment planning, all information will be used only for group statistical analyses. All study participants will be told the expected duration of the study and informed that subjects' consent can be withdrawn at any time, at no risk to having other treatment in that clinical setting withheld. Alternatives to participation are also noted in the consent forms. The consent form will clearly state that child abuse will be reported to appropriate authorities. Sample consent form is attached in **Appendix E.**

Teenager Assent

OPRR regulations do not require written assent and local IRB policies, which vary by site, will prevail. When required, formal assent will be obtained from all participating adolescents during the study. A sample Assent Form is presented in **Appendix E**. It is important to avoid coercion in obtaining the teenager's assent; study personnel "assenting" the teenager must be sensitive to verbal and non-verbal cues from the teenager about reluctance to participate. For this reason, assent will be established by a clinician skilled in working with teenagers. A witness will be present when obtaining the teenager's written or verbal assent to participate in the study, and this will be documented in a manner similar to that in which a witness signs the parent's consent.

Given increased prevalence of conduct problems in adolescents with MDD and normative conflicts over separation/individuation themes, occasional opposition to authority, defiance, and negativism is anticipated. If a patient refuses a given component of the study at one point in time, he/she will be offered the opportunity to "make up" treatment. However, if a patient/parent refuses participation, i.e., withdraws consent, an early termination visit will be scheduled and the patient/family will be referred for community care.

11.2. Potential Risks

To monitor potential risks, clinicians will carefully assess patients for the emergence of adverse events. Using clinical interview procedures, side effects will be monitored, intensively at first, and then at longer yet appropriate intervals during the maintenance stage of treatment. Subjects in all study arms will be followed on a regular basis, and should conditions become apparent to the examiners/interviewers that indicate that the teenager is experiencing significant difficulties as a consequence of the treatment, then appropriate measures, such as emergency triage, hospitalization, and medication/CBT discontinuation will be taken.

Specific risks are those which are normally seen in standard clinical practice, and include the risks of violation of confidentiality, adverse effects of medications, or possible negative effects of psychotherapeutic procedures. Risks associated with assessment procedures, psychosocial treatment and medication are as follows: (a) Patients could develop mild to moderate emotional discomfort or frustration associated with psychiatric interviewing or filling out questionnaires; (b) patients will likely experience subjective distress during CBT treatment and their reactions will be closely monitored and addressed therapeutically. To prevent imminent subject attrition, ASAP sessions are available to manage situations that are outside the study protocol. In the unlikely event that a subject manifests unusually high levels of distress, suggesting prohibitive side effects or intolerance of study treatments, or requires more than the allowable number of ASAP visits, he or she will be withdrawn from the study by the PI in conjunction with the ASAP panel; (c) while FLX is generally well tolerated, side effects do occur. The most commonly reported side effects are: nausea, tremor, overstimulation, headache, and gastrointestinal symptoms. Side effects are dose-dependent, and dose of drug will be titrated to minimize adverse events; (d) one fourth of the treatment population will be exposed to a potentially inactive treatment (pill PBO).

In the case of nonresponse to pill PBO in Stage I, patients will be given open treatment for 12 weeks. In the case of relapse within 3 months after a positive response to PBO treatment in Stage I, patients will be given open treatment. Open treatment will consist of 12 weeks of CBT, medication with FLX or COMB, depending on patient preference.

In cases where danger to self or others is identified and cannot be managed by study procedures, including ASAP, the patient will be withdrawn from the study and clinically appropriate emergency services procedures will be implemented. If previously undocumented sexual or physical abuse is discovered during eligibility assessment, we will implement standard procedures for notifying the Department of Social Services (DSS), and defer further evaluation until the teenager has been released from DSS review. If DSS involvement is identified or mandated at any point during the study, the teenager may or may not be continued in treatment depending on what is in the best interests of the teenager. This decision will be made by the Principal Investigator and treating clinician at the site in coordination with the patient's principle caregivers and the Caseness or ASAP Panels, depending on stage of the study.

All of the data generated in this project are being collected for research purposes. However, since this is a treatment outcome study, research data will be used to guide treatment. All clinically relevant data will (after written request by a subject's parent) be made available to licensed clinicians at the conclusion of study participation at the parent's request. Otherwise, all subject data will be confidential. In particular, we will take the following steps to minimize risks to confidentiality at each site: (a) Interview protocols and case record forms will be kept in a locked site; (b) subjects will be identified by number only; (c) data tapes and disks will be kept in locked storage in locked rooms; (d) data will be entered directly into files that will be password protected; (e) computer files and forms sent to the data center will carry only subject numbers for case identification. All project staff will be trained in the importance of confidentiality, and will promise in writing to protect subject confidentiality. Five years following the conclusion of the study, all audiotapes will be destroyed. If the results of the study are published, data which might reveal the identity of any particular subject will be disguised.

To minimize risks of the forced disclosure of information through court action or legal proceedings, each site will obtain a Certificate of Confidentiality for all study participants -- this will protect all research records (but not clinical records). Given the nature of this study and data collected, the Certificate of Confidentiality will protect research data from forced disclosure to a party in a custody hearing, criminal justice authorities investigating a parent, etc.

Ongoing safety assurance for study Participants will be addressed through various clinical panels and a safety monitoring committee, which will be responsible for reviewing safety issues and treatment issues for difficult cases.

11.3. Potential Benefits

Patients in the treatment study will benefit from receiving a comprehensive evaluation and well-delivered treatment for MDD. There are no commonly accepted "treatments of choice" for MDD in young people, although patients could choose to receive CBT (difficult to find) and/or non-FDA-approved pharmacotherapy outside of the research protocol. Information from this study will directly benefit patients by guiding appropriate treatment planning. It will be of general benefit through adding to the body of knowledge about the etiopathogenesis and treatment of childhood-onset mental illness. Patients in particular may benefit from knowing that they have potentially contributed to improving the care of children with similar problems.

Balance of Risks and Benefits

Apart from the risk of receiving an inactive treatment (pill PBO), this project only entails the modest risks involved in keeping confidential information with a coded identification number and the risks associated with clinically accepted treatments for MDD, and the benefits include both state-of-the-art assessment and treatment for the subjects and potential benefits for future families. Hence, it is felt that the benefits outweigh risks.

Reimbursement of Subjects

To minimize the financial burden on families and to maximize the likelihood of compliance (and therefore of benefit) with treatment, we also provide modest reimbursement for travel costs, time and parking for patients in all three study stages at the rate of $10 per clinic visit. Reimbursing out-of-pocket expenses also may increase the likelihood that low income families will participate, which in turn will increase the representativeness of the sample and generalizability of the results. All subjects/families will receive $100 for completing each assessment.

Consultation with the Office for Protection from Research Risks (OPRR), NIH

Given the public importance of this study, and its relevance to the mission of the National Institute of Mental Health to advance children's mental health through research, the Coordinating Center with NIMH staff will discuss the protocol and consent procedures with OPRR staff to ensure that consent procedures are appropriate, and that the proposed research adheres to OPRR guidelines and ethical standards. However, final determination of the appropriateness of the proposed research lies with individual IRBs at participating institutions.

12. References

1. Carlson G. Identifying prepubertal mania. J Am Acad Child Adolesc Psych 1995;34:750-53.
2. Angold A, Worthman CW. Puberty onset of gender differences in rates of depression: a developmental, epidemiologic and neuroendocrine perspective. J Affect Disord 1993;29:145-58.
3. Lewinsohn PM, Hops H, Roberts RE, et al. Adolescent psychopathology: I. Prevalence and incidence of depression and other DSM-III--R disorders in high school students. J Abnorm Psychol 1993;102:133-44.
4. Kovacs M, Obrosky DS, Gatsonis C, Richards C. First-episode major depressive and dysthymic disorder in childhood: clinical and sociodemographic factors in recovery. J Am Acad Child Adolesc Psychiatry, 1997;36:777-84.
5. Lewinsohn PM, Rohde P, Seeley JR, Hops H. Comorbidity of unipolar depression: I. Major depression with dysthymia. J Abnorm Psychol 1991;100:205-13.
6. Lewinsohn PM, Rohde P, Seeley JR, Fischer SA. Age-cohort changes in the lifetime occurrence of depression and other mental disorders. J Abnorm Psychol 1993;102:110-20.
7. Pine DS, Cohen P, Gurley D, Brook J, Ma Y. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. Arch Gen Psychiatry 1998;55:56-64.
8. Birmaher B, Ryan ND, Williamson DE, Brent DA, Kaufman J. Childhood and adolescent depression: a review of the past 10 years. Part II. J Am Acad Child Adolesc Psychiatry 1996;35:1575-83.
9. Rice DP, Miller LS. The economic burden of affective disorders. Br J Psychiatry Suppl 1995;27:34-42.
10. Simon G, Ormel J, VonKorff M, Barlow W. Health care costs associated with depressive and anxiety disorders in primary care. Am J Psychiatry 1995;152:352-7.
11. Wells K, Sturm R, Sherbourne C, Meredith L. Caring for Depression. Cambridge, MA: Harvard University Press, 1996.
12. Burns BJ, Costello EJ, Angold A, et al. Children's mental health service use across service sectors. Health Affairs 1995;14:147-59.
13. Angold A, Messer SC, Stangl D, et al. Perceived parental burden and service use for child and adolescent psychiatric disorders. Am J Public Health 1998;88*:*75-80.
14. Brent DA Risk factors for adolescent suicide and suicidal behavior: mental and substance abuse disorders, family environmental factors, and life stress. Suicide Life Threat Behav, 1995;25(Suppl):52-63.
15. Hoberman HM, Clarke GN, Saunders SM. Psychosocial interventions for adolescent depression: issues, evidence, and future directions. Prog Behav Modif 1996;30:25-73.
16. Reinecke MA, Ryan NE, DuBois DL. Cognitive-behavioral therapy of depression and depressive symptoms during adolescence: a review and meta-analysis. J Am Acad Child Adolesc Psychiatry 1998;37:26-34.
17. Brent DA, Holder D, Kolko D, et al. A clinical psychotherapy trial for adolescent depression comparing cognitive, family, and supportive therapy. Arch Gen Psychiatry 1997;54:877-85.
18. Lewinsohn PM, Clarke GN, Rohde P. Psychological Approaches to the Treatment of Depression in Adolescents. New York: Plenum Press, 1994:309-44.
19. Jensen PS, Ryan ND, Prien R. Psychopharmacology of child and adolescent major depression: Present status and future directions. J Child Adolesc Psychopharmacol 1992;2:31-45.
20. Birmaher B, Ryan ND, Williamson DE, et al. Childhood and adolescent depression: a review of the past 10 years. Part I. J Am Acad Child Adolesc Psychiatry, 1996;35:1427-39.
21. Emslie GJ, Rush AJ, Weinberg WA, et al. Recurrence of major depressive disorder in hospitalized children and adolescents. J Am Acad Child Adolesc Psychiatry 1997;36:785-92.
22. Ryan ND. The pharmacologic treatment of child and adolescent depression. Psychiatr Clin North Am 1992;15:29-40.

23. Ryan ND. Pharmacological treatment of child and adolescent major depression. Encephale 1993;19:67-70.
24. Jensen PS, Vitiello B, Leonard HL, Laughren TP. Child and adolescent psychopharmacology: expanding the research base. Psychopharmacology 1994;30:3-8.
25. Emslie GJ, Rush AJ, Weinberg WA, et al. Fluoxetine in child and adolescent depression: acute and maintenance treatment. Depress Anxiety 1998;7:32-9.
26. Thase ME, Greenhouse JB, Frank E, et al. Treatment of major depression with psychotherapy or psychotherapy- pharmacotherapy combinations. Arch Gen Psychiatry 1997;54:1009-15.
27. Arnold LE, Abikoff HB, Cantwell DP, et al. National Institute of Mental Health Collaborative Multimodal Treatment Study of Children with ADHD (the MTA). Design challenges and choices. Arch Gen Psychiatry 1997;54:865-70.
28. Elkin I, Parloff MB, Hadley SW, Autry JH. NIMH Treatment of Depression Collaborative Research Program. Background and research plan. Arch Gen Psychiatry 1995;42:305-16.
29. Elkin I, Shea MT, Watkins JT, et al. National Institute of Mental Health Treatment of Depression Collaborative Research Program. General effectiveness of treatments. Arch Gen Psychiatry 1989;46:971-82; discussion 983.
30. Barber JP, Muenz LR. The role of avoidance and obsessiveness in matching patients to cognitive and interpersonal psychotherapy: empirical findings from the treatment for depression collaborative research program. J Consult Clin Psychol 1996;64:951-8.
31. Imber SD, Pilkonis PA, Sotsky SM, et al. Mode-specific effects among three treatments for depression. J Consult Clin Psychol 1990;58:352-9.
32. Sotsky SM, Glass DR, Shea MT, et al. Patient predictors of response to psychotherapy and pharmacotherapy: findings in the NIMH Treatment of Depression Collaborative Research Program. Am J Psychiatry 1991;148:997-1008.
33. Elkin I, Gibbons RD, Shea MT, et al. Initial severity and differential treatment outcome in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. J Consult Clin Psychol 1995;63:841-7.
34. Kernick DP. Which antidepressant? A commentary from general practice on evidence-based medicine and health economics. Br J Gen Pract 1997;47:95-8.
35. Sackett D, Richardson W, Rosenberg W, Haynes B. Evidence-Based Medicine. London: Churchill Livingston, 1997.
36. McMaster University, Faculty of Health Sciences. How to teach evidence-based clinical practice, '99. Available at <http://hiru.hirunet.mcmaster.ca/ebm/>.
37. Hoagwood K, Hibbs E, Brent D, Jensen P. Introduction to the Special Section: efficacy and effectiveness in studies of child and adolescent psychotherapy. J Consul Clin Psychol 1995;63:683-7.
38. Frances AJ, Kahn DA, Carpenter D, Docherty JP, Donovan SL. The Expert Consensus Guidelines for treating depression in bipolar disorder. J Clin Psychiatry 1998;59(Suppl 4):73-9.
39. March J, Frances A, Kahn D, Carpenter D. Expert consensus guidelines: treatment of obsessive-compulsive disorder. J Clin Psychiatry, 1997;58(Suppl 4):1-72.
40. Sturm R, Wells KB. How can care for depression become more cost-effective? JAMA 1995;273:51-8.
41. Boyer WF, Feighner JP. The financial implications of starting treatment with a selective serotonin reuptake inhibitor or tricyclic antidepressant in drug-native patients. In: Johnson B, Rosenbaum JF, eds. Health Economics of Depression. Chichester: John Wiley and Sons, 1993:65-76.
42. Jacobson NS, Christensen A. Studying the effectiveness of psychotherapy. How well can clinical trials do the job? Am Psychol 1996;51:1031-9.
43. Jacobson NS, Hollon SD. Prospects for future comparisons between drugs and psychotherapy: lessons from the CBT-versus-pharmacotherapy exchange. J Consult Clin Psychol 1996;64:104-8.
44. Sanderson WC, Barlow DH. Research strategies in clinical psychology. In: Walker C, ed. Clinical Psychology: Historical and Research Foundations. New York: Plenum Press, 1991:37-49.
45. March J, Curry J. The prediction of treatment outcome. J Abnorm Child Psychol 1998;26:39-52.

46. Maxwell S, Delaney H. Designing Experiments and Analyzing Data: A Model Comparison Perspective. Belmont, CA: Wadsworth, 1990.
47. Pocock S. Clinical Trials: A Practical Approach. New York: Wiley/Liss, 1983.
48. Prien R, Robinson D. Clinical Evaluation of Psychotropic Drugs: Principles and Guidelines. New York: Raven Press, 1994.
49. Conners K. Methodology of antidepressant drug trials for treating depression in adults. J Child Adolesc Psycopharmacol 1992;2:11-22.
50. Arnold L. Design and methodology issues for clinical treatment trials in children and adolescents. Psychopharmacol Bull 1993;29:3-4.
51. Klein D. Control groups in pharmacotherapy and psychotherapy evaluations. Treatment 1997;1:http://journals.apa.org/treatment/vol1/97_a1.html.
52. Parloff M. Placebo controls in psychotherapy research: a sine qua non or a placebo for research problems? J Consul Clin Psychol 1996;54:79-87.
53. Costello EJ, Benjamin R, Angold A, Silver D. Mood variability in adolescents: a study of depressed, nondepressed and comorbid patients. J Affect Disord 1991;23:199-212.
54. Rintelmann JW, Emslie GJ, Rush AJ, et al. The effects of extended evaluation on depressive symptoms in children and adolescents. J Affect Disord 1996;41:149-56.
55. Lewinsohn PM, Clarke GN, Seeley JR, Rohde P. Major depression in community adolescents: age at onset, episode duration, and time to recurrence. J Am Acad Child Adolesc Psychiatry, 1994;33:809-18.
56. Emslie GJ, Rush AJ, Weinberg WA, et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. Arch Gen Psychiatry 1997;54:1031-7.
57. Kraemer HC, Pruyn JP. The evaluation of different approaches to randomized clinical trials. Report on the 1987 MacArthur Foundation Network I Methodology Workshop. Arch Gen Psychiatry 1990;7:1163-9.
58. Gibbons RD, Hedeker D, Elkin I, et al. Some conceptual and statistical issues in analysis of longitudinal psychiatric data. Application to the NIMH treatment of Depression Collaborative Research Program dataset. Arch Gen Psychiatry 1993;50:739-50.
59. Hoagwood K, Jensen PS, Petti T, Burns BJ. Outcomes of mental health care for children and adolescents: I. A comprehensive conceptual model. J Am Acad Child Adolesc Psychiatry 1996;35:1055-63.
60. Birmaher B. Should we use antidepressant medications for children and adolescents with depressive disorders? Psychopharmacol Bull 1998;34:35-9.
61. McCauley E, Myers K, Mitchell J, Calderon R, Schloredt K, Treder R. Depression in young people: Initial presentation and clinical course. J Am Acad Child Adolesc Psychiatry 1993;32:714-22.
62. Stewart JW, Quitkin FM, McGrath PJ, et al. Use of pattern analysis to predict differential relapse of remitted patients with major depression during 1 year of treatment with fluoxetine or placebo. Arch Gen Psychiatry 1998;55:334-43.
63. Greenhouse JB, Stangl D, Kupfer DJ, Prien RF. Methodologic issues in maintenance therapy clinical trials. Arch Gen Psychiatry 1991;48:313-8.
64. Angold A, Rutter M. Effects of age and pubertal status on depression in a large clinical sample. Devel Psychopathol, 1992;4:5-28.
65. Angold A, Costello EJ, Worthman CM. Puberty and depression: the roles of age, pubertal status and pubertal timing. Psychol Med 1998;28:51-61.
66. Agresti A. Categorical Data Analysis. New York: John Wiley & Sons, 1990.
67. Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. Biometrics 1983;39:499-503.
68. Burke KC, Burke JJ, Regier DA, Rae DS. Age at onset of selected mental disorders in five community populations. Arch Gen Psychiatry 1990;47:511-8.
69. Brent DA, Perper JA, Moritz G, et al. Psychiatric risk factors for adolescent suicide: a case-control study. J Am Acad Child Adolesc Psychiatry 1993;32:521-9.

70. Brent DA, Perper JA, Moritz G, et al. Suicide in affectively ill adolescents: a case-control study. J Affect Disord 1994;31:193-202.
71. Peet M. Induction of mania with selective serotonin reuptake inhibitors and tricyclic antidepressants. Br J Psychiatry 1994;164:549-50.
72. Heimann SW, March JS. SSRI-induced mania. J Am Acad Child Adolesc Psychiatry 1996;35:4.
73. Venkataraman S, Naylor MW, King CA. Mania associated with fluoxetine treatment in adolescents. J Am Acad Child Adolesc Psychiatry 1992;31:276-81.
74. Leonard H, Jensen P, Vitiello B, et al. Ethical issues in psychopharmacological treatment research with children and adolescents. In: Hoagwood K, Jensen P, Fisher C, eds. Issues in Mental Health Research with Children and Adolescents. Mahwah, NJ: Lawrence Erlbaum, 1996:73-88.
75. Geller B, Luby J. Child and adolescent bipolar disorder: A review of the past 10 years. J Am Acad Child Adolesc Psychiatry 1997;36:1168-76.
76. Angold A, Costello EJ. Depressive comorbidity in children and adolescents: empirical, theoretical, and methodological issues. Am J Psychiatry 1993;150:1779-91.
77. Dadds MR, Sanders MR, Morrison M, Rebgetz M. Childhood depression and conduct disorder: II. An analysis of family interaction patterns in the home. J Abnorm Psychol 1992;101:505-13.
78. Sanders MR, Dadds MR, Johnston BM, Cash R. Childhood depression and conduct disorder: I. Behavioral, affective, and cognitive aspects of family problem-solving interactions. J Abnorm Psychol 1992;101:495-504.
79. Henggeler SW, Schoenwald SK, Pickrel SG. Multisystemic therapy: Bridging the gap between university- and community-based treatment. Special Section: efficacy and effectiveness in studies of child and adolescent psychotherapy. J Consult Clin Psychol 1995;63:709-17.
80. Lewinsohn PM, Rohde P, Seeley JR. Adolescent psychopathology: III. The clinical consequences of comorbidity. J Am Acad Child Adolesc Psychiatry 1995;34:510-9.
81. Neighbors B, Kempton T, Forehand R. Co-occurrence of substance abuse with conduct, anxiety, and depression disorders in juvenile delinquents. Addict Behav 1992;17:379-86.
82. Bukstein OG, Glancy LJ, Kaminer Y. Patterns of affective comorbidity in a clinical population of dually diagnosed adolescent substance abusers. J Am Acad Child Adolesc Psychiatry 1992;31:1041-5.
83. Kaminer Y, Tarter RE, Bukstein OG, Kabene M. Comparison between treatment completers and noncompleters among dually diagnosed substance-abusing adolescents. J Am Acad Child Adolesc Psychiatry 1992;31:1046-9.
84. Henggeler SW. Multisystemic treatment of serious juvenile offenders: implications for the treatment of substance-abusing youths. NIDA Res Monogr 1993;137:181-99.
85. Kranzler HR, Kadden RM, Burleson JA, et al. Validity of psychiatric diagnoses in patients with substance use disorders: Is the interview more important than the interviewer? Compr Psychiatry 1995;36:278-88.
86. Tsuang D, Cowley D, Ries R, Dunner DL, Roy-Byrne PP. The effects of substance use disorder on the clinical presentation of anxiety and depression in an outpatient psychiatric clinic. J Clin Psychiatry 1995;56:549-55.
87. Brent DA, Perper JA, Moritz G, et al. Familial risk factors for adolescent suicide: a case-control study. Acta Psych Scand 1994;89:52-8.
88. Rickels K, Smith WT, Glaudin V, et al. Comparison of two dosage regimens of fluoxetine in major depression. J Clin Psychiatry 1985;46:38-41.
89. Bennie EH, Mullin JM, Martindale JJ. A double-blind multicenter trial comparing sertraline and fluoxetine in outpatients with major depression. J Clin Psychiatry 1995;56:229-37.
90. Nierenberg AA, McLean NE, Alpert JE, et al. Early nonresponse to fluoxetine as a predictor of poor 8-week outcome. Am J Psychiatry 1995;152:1500-3.
91. Fava M, Rosenbaum JF, Cohen L, et al. High-dose fluoxetine in the treatment of depressed patients not responsive to a standard dose of fluoxetine. J Affect Disord 1992;25:229-34.
92. Lewinsohn PM, Clarke GN, Hops H, Andrews JA. Cognitive-behavioral treatment for depressed adolescents. Behav Ther, 1990;21:385-401.

93. Clarke G, Hops H, Lewinsohn PM, et al. Cognitive-behavioral group treatment of adolescent depression: prediction of outcome. Behav Ther 1992;23:341-54.
94. Becker RE, Heimberg RG, Bellack AS. Social skills training treatment for depression. New York: Pergamon Press, 1987:112.
95. Nezu AM. Cognitive appraisal of problem solving effectiveness: relation to depression and depressive symptoms. J Clin Psychol 1986;42:42-8.
96. Kempton T, van Hasselt VB, Bukstein OG, Null JA. Cognitive distortions and psychiatric diagnosis in dually diagnosed adolescents. J Am Acad Child Adolesc Psychiatry 1994;33:217-22.
97. Garber J, Hollon SD. Universal versus personal helplessness in depression: belief in uncontrollability or incompetence? J Abnorm Psychol 1980;89:56-66.
98. McCauley E, Mitchell JR, Burke P, Moss S. Cognitive attributes of depression in children and adolescents. J Consult Clin Psychol 1988;56:903-8.
99. Curry JF, Craighead WE. Attributional style in clinically depressed and conduct disordered adolescents. J Consult Clin Psychol 1990;58:109-15.
100. Clarke GN. Improving the transition from basic efficacy research to effectiveness studies: methodological issues and procedures. J Consult Clin Psychol 1995;63:718-25.
101. Rey JM, Starling J, Wever C, et al. Inter-rater reliability of global assessment of functioning in a clinical setting. J Child Psychol Psychiatry Allied Discipl 1995;36:787-92.
102. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol 1991;59:12-9.
103. SAS/STAT User's Guide, Version 6, 4th ed. Cary, NC: SAS Institute Inc., 1990.
104. StatXact 3 for Windows. Cambridge, MA: CYTEL Software Corporation, 1995.
105. Koch GG, Edwards SE. Clinical efficacy trials with categorical data. In: Peace KE, ed. Biopharmaceutical Statistics for Drug Development. New York: Marcel Dekker, 1987.
106. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
107. Cox DR. Regression models and life tables. J R Stat Soc B 1972;34:187-220.
108. Cox DR. Partial likelihood. Biometrika 1975;62:269-76.
109. Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika, 1986;73:13-22.
110. Laird NM, Ware JH. Random-effects models for longitudinal data. Biometrics 1982;38:963-74.
111. SAS/STAT Software: Changes and Enhancements through Release 6.12. Cary, NC: SAS Institute, Inc., 1997.
112. Schall R. Estimation in generalized linear models with random effects. Biometrika 1991;40:917-27.
113. Breslow NE, Clayton DG. Approximate inference in generalized linear mixed models. J Am Stat Assoc 1993;88:9-25.
114. Wolfinger R. The GLIMMIX SAS Macro. Cary, NC: SAS Institute, Inc., 1993.
115. Freedman LS, Graubard BI, Schatzkin A. Statistical validation of intermediate endpoints for chronic diseases. Stat Med 1992;11:167-78.
116. Susser M, ed. Causal Thinking in the Health Sciences. New York: Oxford University Press, 1973.
117. Gold MR, Siegel JE, Russell, LB, Weinstein MC, eds. Cost Effectiveness in Health and Medicine. New York: Oxford University Press, 1996.
118. Kamlet MS, Paul N, Greenhouse J, et al. Cost utility analysis of maintenance treatment for recurrent depression. Contr Clin Trials 1995;16:17-40.
119. Doubilet, P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using monte carlo simulation. Med Decis Making. 1985;5:157-177.
120. Zarkin GA, Bala MV, Calingaert B, VanderLugt JT. The cost-effectiveness of ibutilide versus electrical cardioversion in the conversion of atrial fibrillation and flutter to normal rhythm. Am J Manag Care 1997;3:1387-94.
121. Zarkin G, Bala M, Wood L, et al. Estimating the cost effectiveness of atovaquone versus intravenous pentamidine in the treatment of mild-to-moderate *Pneumocystis carinii* pneumonia. Pharmacoeconomics 1996;9:525-34.

122. Beck A, Ward C, Mendelson M. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71.
123. Derogatis L, Lipman R, Covi L. SCL-90: An outpatient psychiatric rating scale-Preliminary Report. Psychopharmacol Bull 1973;9:13-7.
124. Derogatis LR, Spencer PM. Administration Procedures: BSI Manual-I, Clinical Psychometric Research. Baltimore: Johns Hopkins University School of Medicine, 1982.
125. Costello EJ, Angold A, March J, Fairbank J. Life events and post-traumatic stress: the development of a new measure for children and adolescents. Psychol Med 1998;28:1275-88.
126. Angold A, Patrick MKS, Burns BJ, Costello EJ. The Child and Adolescent Impact Assessment (CAIA): Parent Interview Version 2.0. Durham: Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, 1996.
127. Ascher B, Farmer E, Burns B, Angold A. The child and adolescent services assessment (CASA): description and psychometrics. J of Emotional and Behavioral Disorders 1996; vol. 4:12-20.
128. Farmer E, Angold A, Burns, B, Costello, J. Reliability of self-reported service use: test-retest consistency of children's responses to the child and adolescent services assessment (CASA). J Child and Family Studies 1994;3:307-315.
129. Kovacs M. The Children's Depression Inventory (CDI). Psychopharmacol Bull 1985;21:995-8.
130. Kovacs M. Manual: The Children's Depression Inventory. Toronto: MultiHealth Systems, 1995.
131. Guy W. ECDEU Assessment Manual for Psychopharmacology, 2nd ed. DHEW Publication No. (ABM) 76-388). Washington, DC: U.S. Government Printing Office, 1976.
132. Bird H, Gould M. The use of diagnostic instruments and global measures of functioning in child psychiatry epidemiologic studies. In: Verhulst FC, Koot HM, eds. The Epidemiology of Child and Adolescent Psychopathology. Oxford: Oxford University Press, 1995:86-103.
133. Conners CK. Manual for the Conners' Rating Scales. Toronto: MultiHealth Systems, 1990.
134. Loney J, Milich R. Hyperactivity, inattention, and aggression in clinical practice. In: Wolraich M, Routh DK, eds. Advances in Developmental and Behavioral Pediatrics. Greenwich, CT: JAI Press, 1982:113-147.
135. Conners CK, Wells K. Conners-Wells Adolescent Self-Report Scale: item selection and replication of the factor structure. Unpublished manuscript, Duke University Medical Center, 1995.
136. Dishion T. The peer context of troublesome child and adolescent behavior. In: Leone PE, ed. Understanding Troubled and Troubling Youth: Multiple Perspectives. Thousand Oaks, CA: Sage, 1990.
137. Lahey BB, Applegate A, McBurnett K, et al. DSM-IV Field Trials for attention-deficit hyperactivity disorder in children and adolescents. Am J Psychiatry 1994;151:1673-85.
138. Spanier G. Measuring dyadic adjustment: new scales for assessing the quality of marriage and similar dyads. J Marriage Family 1976;38:15-28.
139. Skinner H. Self-report instruments for family assessment. In: Jacob T, ed. Family Interaction and Psychopathology. New York: Plenum Publishing Corporation, 1987.
140. Skinner H, Steinhauer P, Santa-Barbara J. The Family Assessment Measure. Can J Commun Mental Health 1983;2:91-105.
141. Carroll BJ, Fielding JM, Blashki TG. Depression rating scales: a critical review. Arch Gen Psych 1973;28:361-6.
142. Foley RM, Epstein MH. Evaluation of the Homework Problem Checklist with students with behavior disorders. Spec Serv Schools 1993;1:79-90.
143. Beck A, Weissman A, Lester D, Trexler L. The measurement of pessimism: the hopelessness scale. J Consult Clin Psychol 1974;42:861-5.
144. Spirito A, Stark LJ, Williams C. Development of a brief coping checklist for use with pediatric populations. J Pediatr Psychol 1987;13:555-74.
145. Angold A. Structured assessments of psychopathology in children and adolescents. In: Thompsen C, ed. The Instruments of Psychiatric Research. Chichester: Wiley, 1989:271-304.
146. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997;36:980-8.

147. Patterson GR. Coercive Family Process. Eugene, OR: Castalia, 1982.
148. Rothbaum F, Weisz J. Parental caregiving and child externalizing behavior in non-clinical samples: a meta-analysis. Psych Bull 1994;116:55-74.
149. Loeber R, Stouthamer-Loeber M, van Kammen WB, Farrington D. Initiation, escalation, and desistence in juvenile offending and their correlates. J Crim Law Criminol 1991;82:36-82.
150. Keenan K, Loeber R, Zhang Q, Stouthamer-Loeber M, van Kammen WB. The influence of deviant peers on the development of boys' disruptive and delinquent behavior: a temporal analysis. Devel Psychopath 1995;7:715-26.
151. Colder CR, Lochman JE, Wells KC. The moderating effects of children's fear and activity level on relations between parenting practices and childhood symptomatology. J Abnorm Child Psychol 1997;25:251-63.
152. March JS, Parker JD, Sullivan K, Stallings P, Conners CK. The Multidimensional Anxiety Scale for Children (MASC): factor structure, reliability, and validity. J Am Acad Child Adol Psychiatry 1997;36:554-65.
153. First M, Spitzer R, Gibbon M, Williams J. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). Washington, DC: APA Press, 1997.
154. Harter S. Manual for the Self-Perception Profile for Children. Unpublished manuscript, University of Denver, 1985.
155. Harter S. The Self-Perception Profile for Adolescents. Unpublished manuscript, University of Denver, 1988.
156. Dorn LD, Sueman EJ, Nottelman ED, Inoff-Germain G. Perceptions of puberty: adolescent, parent, and health care personnel. Devel Psychol 1990;26, 322-9.
157. Stern RA, Prochaska JO, Velicer WF, Elder JP. Stages of adolescent cigarette smoking acquisition: measurement and sample profiles. Addict Behav 1987;12:319-29.
158. Velicer WF, Hughes SL, Fava JL, Prochaska JO, DiClemente CC. An empirical typology of subjects within stage of change. Addict Behav 1995;20:299-320.
159. Wechsler D. Wechsler Individual Achievement Test--Manual. San Antonio: The Psychological Corporation, 1992.
160. Wechsler D. Wechsler Intelligence Scale for Children, 3rd ed. San Antonio: The Psychological Corporation, 1991.
161. Lavori, P., E. Laska, et al. (1994). Statistical issues for the clinical evaluation of psychotropic drugs. Clinical Evaluation of Psychotropic Drugs: Principles and Guidelines. R. Prien and D. Robinson. New York, Raven Press: 139-160.
162. Pocock, S. (1983). Clinical Trials: A Practical Approach. New York, Wiley/Liss.
163. Holmbeck, G. N. (1997). “Toward terminological, conceptual, and statistical clarity in the study of mediators and moderators: examples from the child-clinical and pediatric psychology literatures.” Journal of Consulting & Clinical Psychology 65(4): 599-610.
164. March, J. and J. Curry (1998). “The prediction of treatment outcome.” Journal of Abnormal Child Psychology 26(1): 39-52.

13. Appendix A. List of Drug Classes for Inclusion or Exclusion of Subjects[a]

Drug Class	If Episodic Use [b]	If Chronic Use [c]
Anorexics	N	N
Antacids	Y	Y
Antiarrythmics	N	N
Anti-asthma agents		
Systemic, ventilator	Y	Y
Topical	Y	Y
Intal inhaler	Y	Y
Antibiotics	Y	Y
Anticoagulants	N	N
Anti-diarrheas	Y	N
Antihistamines for allergies (non-selective or selective H1 antagonists)	Y	Y
Anti-hypertensives	N	N
Anti-nauseants	Y	N
Anti-seizure medications	N	N
Aspirin	Y	Y
Birth Control (e.g., BCP, Norplant, Depo-Provera)	Y	Y
Cough/Cold preparations	Y	N
Diuretics	N	N
Herbal Psychotropic Preparations Anxiolytics (e.g. valerian) Antidepressants (e.g. St. John's Wort) Anti-hyperactives (e.g. pycnogenol) Stimulants (e.g. Metabolife) Memory Aids (e.g. Ginko Biloba)	N	N
Other Non-psychotropic Herbal Preparations	Y	Y
H2 blockers (e.g., anti-ulcer meds)	Y	Y
Hormones (other than BCPs)	Y	N
Hypoglycemic agents	N	N
Insulin	N	Y
Laxatives	Y	Y
Narcotics for pain management	Y	N
Non-narcotic analgesics	Y	Y
Other psychotropic medication	N	N
Sedative-Hypnotics	Y	N
Melatonin	Y	Y
Trazadone	N	N
Chloral hydrate	Y	N
Diphenhydrame (e.g. Tylenol PM)	Y	N
Benzodiazapines	N	N
Zolpidem (Ambien)	Y	N
Steroids	Y	Y[d]
NSAIDS	Y	Y
Tryptophan	N	N
Vitamins	Y	Y

[a] Post-randomization, no subject shall be excluded for use of medications either episodic or chronic unless the condition/medication makes TADS treatment ethically unacceptable or unfeasible, but use of such medications should be tracked on the CML and via the CASA.

[b] Brief (less than 2 weeks) of OTC or physician prescribed medications.

[c] Review by Caseness Panel if questionable.

[d] If taken before study initiation for a non-mental health indication and dose is stabilized:

Y = subject may be included in study

N = subject must be excluded from the study before randomization. Use documented after randomization or, if problematic with respect to study treatments, managed according to ASAP and/or early termination procedures.

14. Appendix B. Timetable/Proposed Work Plan Year 1

Planning Phase	10/98	11/98	12/98	1/99	2/99	3/99	4/99	5/99	6/99	7/99	8/99	9/99	10/99
Award	x												
Sites Selected													
Establish site contracts				x	x	x	x						
Investigator/Training meeting													x
Protocol development		x	x	x	x	x	x	x					
Prepare ICF and NIMH approve			x	x	x								
Prepare CBT manual			x	x	x	x	x	x					
Implement feasibility study									x	x	x	x	
Training via conference call								x	x				
Pilot manuals and forms									x	x	x	x	
Feasibility report												x	
Develop and maintain Web site							x	x	x	x	x	x	
Prepare Manual of Operations								x	x	x	x		
Program and test randomization scheme										x	x	x	
Obtain and label drugs								x	x	x	x		
Pharmacy shipments start									x				
Data management preparations													
Data forms development/redevelopment				x	x	x	x	x	x	x	x	x	x
Develop tracking method for forms							x	x	x	x	x	x	x
Design interim reports								x	x	x	x		
Formulate quality control procedures						x	x	x	x	x	x	x	x

Timetable/Proposed Work Plan Year 2-6

Implementation	10/99	01-06/00	07-12/00	01-06/01	07-12/01	01-06/02	07-12/02	01-06/03	07-12/03	01-6/04	07-12/04
Enrollment & Treatment											
Recruitment & Screening		x	x	x	x	x					
Stage 1 Treatment		x	x	x	x	x					
Stage II Treatment Consolidation			x	x	x	x	x				
Stage III Treatment Maintenance			x	x	x	x	x				
Stage IV Follow-up				x	x	x	x	x	x	X	
Data											
Entry		x	x	x	x	x	x	x	x		
Editing/Query		x	x	x	x	x	x	x	x		
Analysis					x	x	x	x	x	x	
Manuscripts and Presentations						x	x	x	x	x	x

15. Appendix C. Description of Assessment Measures

Affective Disorders Screen (ADS). Developed for this study, the ADS is a continuous measure that covers DSM-IV major depression, hypomania and mania as a patient self-report form and, subsequently, clinician-validated fashion.

Adolescent Medical History (AMH). This screening interview will be used to obtain information about the teenager's past medical history and treatments. The interview and form will be completed by a physician before the physical examination at Gate B.

Beck Depression Inventory (BDI). The Beck Depression Inventory (BDI) is a 21 item adult self-report inventory, to assess presence and severity of parental depressive symptoms.[122]

Beck Hopelessness Scale (BHS). A 20-item self report measure of hopelessness which has been found to be a predictor of suicidal risk.[143]

Brief Symptom Inventory (BSI), is the short form of the SCL-90-R® instrument, a well validated measure of general psychopathology.[123, 124] A parent version will be used for this study.

The Child and Adolescent Impact Assessment (CAIA) asks parents about 20 potential perceived burdens—that is problems or difficulties in their own lives (CAIA) that they perceived as being caused or exacerbated by their teenager's depressive disorder or other psychiatric symptoms.[126] The areas covered include expenses and financial difficulties, problems in relationships with family or social network members, restrictions on activities, and decreased feelings of well-being and competence. Items are scored as 0, 1, 2 or 3 depending on the degree of burden (possible scores ranged from 0-59). Rules for assigning these scores are contained in the CAIA schedule. Factor analyses have indicated that one major factor predominates in the CAIA in both general population and severely disturbed clinical samples, accounting for about 30% of the items' variance. Coefficient alpha for the scale in this sample was .88. Two-week stability of the CAIA in a small (N=19) clinical sample was adequate (ICC=.60). Construct validity of the CAIA is indicated by significant mean differences in CAIA scores between groups with varying rates and severity of psychopathology (.9 (SD=3.3) in the Great Smoky Mountains Study general population sample; 7.4 (SD=7.1) in a teenager guidance clinic sample; and 15.7 (SD=10.1) in a group of seriously emotionally disturbed youth at imminent risk for out-of-home placement.[13]

The Child and Adolescent Services Assessment (CASA) is a self-report instrument developed to assess use of mental health services by children and adolescents ages 8 years to 18 years. Such services are broadly defined to include services provided by a variety of public sectors (e.g., health, mental health, substance abuse, social service, education, juvenile justice); by private providers; and by information, personal, and community resources.[127] Services include efforts to identify, diagnose, or treat emotional, behavioral, or substance-related problems across community and institutional settings. The CASA also examines attitudes toward treatment, out-of-pocket costs for treatment, and perceived barriers to services use. It is face-to-face interview that takes about 20 minutes to complete for a teenager with substantial service use. Both teenager and parent versions have been developed, tested, and used in a variety of studies. The CASA has high retest reliability (k>.80) for intensive services, good reliability (k=.30-.50) for nonprofessional services.[128] A comparison with mental health center records shows 100% agreement for inpatient and 79% agreement overall.[127]

Children's Attributional Style Questionnaire (CASQ). A 48-item self-report scale that measure attributions for positive and for negative events: moderate internal consistency; depressed adolescents make significantly fewer internal, stable, global attributions for positive events than do non-depressed psychiatric controls.[99]

Conners-Wells Adolescent Self-Report Scale-Long (CASS)— This is a 102 item, self-report instrument[135] normed on a representative sample of 2,000 12-18 year olds. The CASS has validated and

reliable factors in six domains: Family problems, emotional problems, conduct problems, cognitive problems, anger control problems, and hyperactivity.

CBT Rationale Acceptance & Expectation for Improvement (CBTE)—Brief questionnaire teen completes at second CBT session to assess his/her understanding of CBT and his/her expectancy about improvement.

Children's Depression Rating Scale, Revised (CDRS). The CDRS-R, which covers 17 symptom areas relevant to pediatric MDD utilizing parent and teenager report, is a well-validated depression rating scale that has received wide use as the primary scalar dependent measure in studies of psychotherapy and medication.

Children's Conflict Behavior Questionnaire (CBQ). A 44-item adolescent and 44-item parent report measuring perceived conflict and negative communication. Re-test reliability is moderate for mother-adolescent and high for father-adolescent. Scores were related to outcome in family therapy in Brent's 1997 outcome study.[17]

Children's Negative Cognitive Error Questionnaire (CNCE). A 24-item self-report measure of cognitive distortions. High internal consistency. Scores were related to outcome in cognitive therapy in Brent's study.

Clinical Global Assessment Scale (CGAS). We will use the CGAS, which is a well-validated global measure of impairment, as our clinician-rated measure of functional impairment due to MDD.[101]

Clinical Global Impression—Severity and Improvement (CGI). We will use the 7-point NIMH CGI[131] Scales to monitor clinical improvement and illness severity as rated by the primary clinician(s) and an independent evaluator.

Concomitant Medication Log (CML). This form is completed at each session as needed by the Study Coordinator (and reviewed by the primary clinician) to record any additional medication that the subject may be receiving during the trial and to ensure that he/she is not receiving any prohibited medications.

Concomitant Treatment Log (CTL). This form is completed at each session as needed by the Study Coordinator (and reviewed by the primary clinician) to record any additional non-medication, psychiatric treatment that the subject may be receiving during the trial and to ensure that he/she is not receiving any prohibited treatments.

Conners Adult ADHD Rating Scale-Long Form (CAARS) . This is a 66-item, self-report instrument normed on a representative sample of adults, with validated and reliable factors in 9 domains plus DSM-IV ADHD scoring and an ADHD index.

Conners Parent Rating Scale-Long Form (CPRS). Widely-used, treatment sensitive, and well-normed (to age 17) instrument containing 93 items and valid factors of conduct, hyperactivity-impulsivity, and attention problems.[133]

Consent Form Questionnaire (CFQ). This is a 13-item questionnaire that assesses parent's and teen's general understanding of research procedures and consent process.

Consumer Satisfaction Questionnaire (CSQ). Based on similar measures used in Treatment of Pediatric OCD and the MTA studies, the consumer satisfaction questionnaire asks the patient and his/her parent about their level of satisfaction with the treatment and the TADS staff.

Cognitive Triad Inventory For Children (CTI)— The CTI is a 36-item self-report questionnaire that will be completed by the teenager. This instrument is used to assess self-perceived competencies and global self-worth in adolescents. The following subscales are derived from the individual items: self-scale, world scale, and future scale. For the TADS study, the items comprising the future subscale have been deleted because of their overlap with information obtained on other self-report questionnaires.

Concomitant Treatment Log (CTL)—A log of concomitant, non-drug psychiatric treatment that patient receives during TADS participation. Maintained by the primary therapist.

Demographics Questionnaires (DEMB/DEMU). We will use a demographic interview with the primary caretaker that will cover all aspects of household status (e.g., who lives in and out of the home, mobility frequency, neighborhood) and contributors to SES (e.g., job, income, education). The demographics measure will be updated at each major assessment point.

Dyadic Adjustment Scale (DYA). The DAS is a 32-item, self-report inventory that contains four empirically validated subscales of marital adjustment.[138]

Dysfunctional Attitudes Scale (DAS). A 40-item self-report measure of underlying beliefs or attitudes that represent cognitive vulnerabilities to depression. The perfectionism factor predicted poorer response in the NIMH collaborative study on treatment of depression.

Family Assessment Measure (FAM), is a parent self-report instrument that provides quantitative indices of family strengths and weaknesses, to the primary caregiver. The FAM is based on a process model of family functioning that integrates different approaches to family therapy and research, including assessments of the following factors: task accomplishment, role performance, communication, affective expression, involvement, control, value, and norms. Summary scores also include: general scale focusing on the family as a system; dyadic relationships scale examining relationships between specific pairs; and a self-rating scale that taps the individual's perception of his/her functioning in the family.[139,140]

HONOSCA (HON). Used in Richard Harrington's large treatment outcome study of CBT with and without an SSRI in Britain, the HONOSCA is a clinician administered general symptom and function measure that has been shown to be treatment sensitive in previous studies of adolescent depression.

Homework Completion Form (HWK). Brief questionnaire that the CBT therapist completes at the end of each CBT session assessing how well the patient has completed the homework assignment.

Independent Evaluator Blindness (IEB). To assess the adequacy of the IE blinding procedure, we will ask the IE to guess group assignment throughout the patient's participation.

Issues Checklist (ICP/ICA). A 44-item list of areas that may lead to conflict or disagreement between parents and adolescents. Moderately good test-retest reliability.

IVRS Randomization Worksheet (IVRS). A checklist that the Study coordinator uses to prepare for the call to the randomization center.

K-SADS. The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) is an exceedingly reliable and valid representation of DSM-IV psychopathology, especially affective disorders, in children and adolescents. The current version of the interview surveys additional disorders not assessed in prior K-SADS, contains improved probes and anchor points, includes diagnosis-specific impairment ratings, generates DSM-III-R and DSM-IV diagnoses, and divides symptoms surveyed into a screening interview and five diagnostic supplements. Interrater agreement in scoring screens and diagnoses is high (range: 93% to 100%). Test-retest reliability kappa coefficients were in the excellent range for present and/or lifetime diagnoses of major depression, any bipolar, generalized anxiety, conduct, and oppositional defiant disorder (.77 to 1.00) and in the good range for present diagnoses of posttraumatic stress disorder and attention-deficit hyperactivity disorder (.63 to .67).[145,146]

Medication Diary (MD). This form is completed by parents/guardians and reviewed at pharmacotherapy treatment sessions to record compliance.

Multidimensional Anxiety Scale for Children (MASC). This Likert-style self-report inventory, which is nationally normed through age 18, inventories key subcomponents of anxiety in children and adolescents.[152] Confirmatory factor analyses replicate the MASC factor structure in the MTA sample.

Internal reliability (Cronbach alpha 0.92), test-retest reliability (ICC > .92) and convergent/divergent validity are satisfactory (J. March, unpublished data).

Personal Experience Screening Questionnaire (PESQ). This is a 40-item self-report questionnaire that ask the teenager about his/her experiences using alcohol and other drugs. This instrument will be used to assess frequency and severity of alcohol and recreational drug use during the study. For the TADS study, the mood items in Part II of this form have been deleted because their overlap with information obtain on other self-report questionnaires.

Pediatric Life Events Screen (PLES). Adapted from the Child and Adolescent Trauma Survey (CATS), which shows excellent psychometric properties, including test-retest reliability, the Pediatric Life Events Scale is a 25-item inventory of major negative life events rated present or absent. Positive events are then rated for affective valence.

Physical Symptoms Checklist (PSC). A self-report checklist completed by the patient every six weeks that identifies symptoms as present or not, and level of severity.

Psychiatric Treatment History Form (PTH). A history of the patient's prior psychiatric treatment completed at baseline by the MD.

Pediatric Quality of Life Scale (PQLQ) (PQ-LES-Q). A pediatric adaptation of Jean Endicott's Q-LES-Q, which the most commonly used well validated quality of life scale found in the adult treatment outcome literature. Pediatric validation studies are underway. Quality of life scale.

Reynolds Adolescent Depression Scale (RADS). The RADS is a 30 item 4-point Likert scale that assesses depressive symptoms in adolescents. It is well suited for screening individuals or large groups of students in schools or clinical settings. Reliability coefficients by grade range from .91-.94, with total sample alpha reliability of .92 and split-half reliability of .91. Six week and 3-month test-retest coefficients are .80 and .79, respectively.

Suicide Ideation Questionnaire (SIQ). This 10-item self-report is done at baseline and each treatment visit to assess suicidal risk factors.

Study Screening Interview (SSI)— This 15-minute screening interview will be conducted at Gate A of the study. The parent will be asked to provide general information about the teenager, such as age, grade, depression history, etc.

Study Screening Log (SSL). This Web site application will begin at the Gate A Phone Screen and will be updated on the Web site at each Screening Gate until the subject is randomized or ruled ineligible for the trial. At Gate A, key demographic data for all subjects screened (whether eligible or ineligible) will be entered into the Screening Log: ID number, age, race, sex, source of referral. Subject status will be updated at each subsequent Screening Gate (i.e., eligible, proceeding to next gate, or randomized vs. ineligible and reason for exclusion).

Stages of Change (SOC). To gauge readiness to engage in treatment, we will use a stages of change measure adapted for the Treatment of Pediatric OCD study. The transtheoretical model of behavior change postulates five distinct, well-defined stages of change: Precontemplation, Contemplation, Preparation, Action, and Maintenance. Each stage has been regarded as reflecting a motivational posture and treated as if it is homogenous with respect to membership.[157,158]

Social Problem Solving Inventory (SPSI). Social Problem-Solving Inventory-Revised. A 70-item self-report measure of problem orientation and problem solving skills. Internal consistency, factorial validity and expected relationships with depression and social skills have been demonstrated in adolescents.

Treatment Assignment Reaction (TAR). At the Orientation Visit, when the patient and parent are informed of treatment assignment, the therapist will record their reactions.

Tanner Staging Form (TSF). A crucial variable in prospective investigations of adolescent participants is determination of physical and sexual maturation. In a multi-informant investigation, Dorn et al.[156] found that when 9-15 year old boys and girls were shown schematic drawings (5 ordinally-scaled drawings/photographs corresponding to the Tanner stages), their self-ratings correlated at r = .77 to .91 with health-care-provider examination Tanner staging. To avoid intrusiveness in examining for sexual maturity, we will employ these self-rated pictures for teenager/adolescent self-report.

Treatment Blindness (Tx Blindness) for Parent and Adolescent (TBP, TBA, TBPT). This form assesses whether or not parents and adolescents are blind to the medication condition of the study. We will have the informants guess which treatment the adolescent is receiving and rate their level of certainty.

Treatment Expectancy (TEP, TEA). Therapist and patient (parent and teenager) expectancies about the usefulness of CBT and medication interventions for depression could influence the outcome of treatment directly or by mediating other potential predictor variables, such as treatment compliance. Consumer satisfaction measures are important indicators of compliance as well as guides to designing more effective treatments. Unfortunately, there are no measures of treatment expectancy or consumer satisfaction that have been psychometrically validated for children and adolescents with depression. Adapting measures currently applied in the AU/Columbia study of OCD treatment outcome, we will ascertain therapist expectancy (both direction and strength of belief) for CBT, FLX, COMB and PBO by provider type (PS or psychopharmacologist).

Wechsler Individual Achievement Test (WIAT). -The WIAT screener consists of three subtests - basic reading, mathematics reasoning, and spelling- of the WIAT Comprehensive battery. The teenager will be given the basic reading subtest at Gate B to evaluate reading skills. Teenager with poor reading skills will be given additional assistance when completing self-report forms.

Wechsler Intelligence Scale for Children--3rd edition (WISC-III). This is the standard intelligence measure for children and adolescents, with extensive renorming in the 3rd edition.[160] Internal consistency within subtests, test-retest reliability, and criterion validity are all excellent. We will perform 2 subtests: -The vocabulary and block design subtests will be administered in the TADS study. If a teenager has a raw score below 6 on either subtest, the entire WISC-III will be performed so that a Full-Scale IQ score can be obtained. Teenager who have undergone IQ testing with the WISC-III in the past three years and can provide a copy of the test results will not be asked to complete the WISC subtests.

16. Appendix D. TADS Data Collection Forms

ABBR	INSTRUMENT/FORM NAME	VERSIONS	DOMAIN
AEL	Adverse Event Log		Tracking
ADS	Affective Disorders Screen		Behavioral
AMH	Adolescent Medical History		Behavioral
ASAP	Adjunct Services Attrition Prevention Log		Tracking
BDI	Beck Depression Inventory (one form, 2 copies will be included in the packet)	1) Mother 2) Father	Environment
BHS	Beck Hopelessness Scale		Behavioral
BSI	Brief Symptom Inventory		Environment
CAIA	Child and Adolescent Impact Assessment -		Systems
CAARS	Conners' Adult ADHD Rating Scale – Long Form (one form, two copies will be included in the packet)	1) Mother 2) Father	Environment
CASA	Child and Adolescent Services Assessment		Systems
CASQ	Modified Children's Attributional Style Questionnaire		Behavioral
CASS	Conners-Wells Adolescent Self-Report Scale-Long		Behavioral
CBQP **CBQM** **CBQF**	Conflict Behavior - Parent about adolescent Conflict Behavior – Adolescent about mother Conflict Behavior – Adolescent about father	1) Parent 2) Adol (mother) 3) Adol (father)	Environment
CBTA	CBT Session Checklist		Tracking
CBTE	CBT Treatment Rationale Acceptance & Expectancy for Improvement		Behavioral; Consumer
CDRS	Children's Depression Rating Scale, Revised		Behavioral
CFQ	Consent Form Questionnaire	1) Parent 2) Adol	Behavioral; Consumer
CGAS	IE Battery: Children's Global Assessment Scale	1) IE Visit	Functioning
CGASt	Treatment Session: Children's Global Assessment Scale	1) PT Visit 2) CBT Visit	Functioning
CGI	IE Battery: Clinical Global Impressions – Severity and Improvement Scores (CGI-S and CGI-I)	1) IE Visit	Behavioral; Functioning
CGIt	Treatment Session: Clinical Global Impressions – Severity and Improvement Scores (CGI-S and CGI-I)	1) PT Visit 2) CBT Visit	Behavioral; Functioning
CML	Concomitant Medication Log		Tracking
CNCE	Children's Negative Cognitive Error Questionnaire		Behavioral
CPRS	Conners' Parent Ratings Scale-Long Version		Behavioral

TADS DATA COLLECTION FORMS
(cont.)

ABBR	INSTRUMENT/FORM NAME	VERSIONS	DOMAIN
CSQP **CSQA**	Consumer Satisfaction Questionnaire, for Parent Consumer Satisfaction Questionnaire, for Adolescent	1) Parent 2) Adolescent	Consumer
CTI	Cognitive Triad Inventory for Children		Behavioral
CTL	Concomitant Treatment Log		Tracking
DAS	Dysfunctional Attitudes Scale		Behavioral
DEMB	Demographics Questionnaire: Baseline		Environment
DEMU	Demographics Questionnaire: Update		Environment
DYA	Dyadic Adjustment Scale		Environment
FAM	Family Assessment Measure-III, General Scale (one form, 2 copies will be included in the packet)	1) Parent 2) Adolescent	Environment
HON	The Health of the Nation Outcome Scale for Children and Adolescents (Honosca)		Behavioral; Functioning
HWK	CBT Homework Completion Form	1) CBT	Tracking
ICP **ICA**	Issues Checklist, for Parent Issues Checklist , for Adolescent	1) Parent 2) Adolescent	Behavioral
IEB	Independent Evaluator Blindness		Behavioral
IVRS	IVRS Randomization Worksheet		Tracking
KSADb	Schedule for Affective Disorders & Schizophrenia for School-Age Children (*Affective Disorders modules)* • Instruction and Interview Booklet *(no data entry)*		Behavioral
KSADt	Schedule for Affective Disorders & Schizophrenia for School-Age Children (*Affective Disorders modules)* • Tally Sheet *(data entry)*		Behavioral
KSADs	Schedule for Affective Disorders & Schizophrenia for School-Age Children (*Affective Disorders modules)* • Summary Sheet *(data entry)*		
KSb	Schedule for Affective Disorders & Schizophrenia for School-Age Children *(excluding Affective Disorders modules)* • Instruction and Interview Booklet *(no data entry)*		Behavioral
KSs	Schedule for Affective Disorders & Schizophrenia for School-Age Children (*Affective Disorders modules)* • Summary Sheet *(data entry)*		Behavioral
MASC	Multidimensional Anxiety Scale for Children		Behavioral
MCL	Medication Count Log -	1) PT	Tracking
MD	Medication Diary	1) PT	Tracking

TADS DATA COLLECTION FORMS
(cont.)

ABBR	INSTRUMENT/FORM NAME	VERSIONS	DOMAIN
PE	Physical Examination		Tracking
PESQ	Personal Experience Screening Questionnaire		Behavioral
PLES	Pediatric Life Events Screen		Behavioral
PQLQ	Pediatric Quality of Life Scale (PQ-LES-Q)		Systems
PSC	Physical Symptoms Checklist		Behavioral
PTO	Pharmacotherapy Office Session Checklist		Tracking
PTP	Pharmacotherapy Phone Session Checklist		Tracking
PTH	Psychiatric Treatment History Form		Behavioral
PMT	Premature Termination Form		Tracking
RADS	Reynolds Adolescent Depression Scale		Behavioral
SAE	Serious Adverse Event Report Form		Tracking
SCF	Study Completion Form		Tracking
SIQ	Suicide Questionnaire		Behavioral
SSI	Study Screening Interview for Gate A		Behavioral
SSL	Study Screening Log		Tracking
SOC	Stages of Change		Consumer
SPSI	Social Problem Solving Inventory-Revised		Behavioral
STAGE	End of Stage Form		Tracking
TAR	Treatment Assignment Reaction		Consumer
TBP **TBA** **TBPT**	Treatment Blindness Question, for Parent Treatment Blindness Question, for Adolescent Treatment Blindness, for Pharmacotherapist *(Medication only conditions)*	1) Parent 2) Adolescent 3) PT Visit	Behavioral
TEP **TEA**	Treatment Expectancy Form, for Parent Treatment Expectancy Form, for Adolescent	1) Parent 2) Adolescent	Behavioral; Consumer
TSF	Tanner Staging Form		Behavioral
WECH	Wechsler Intelligence Scale for Children- 3rd Edition and Wechsler Individual Achievement Test		Behavioral

TADS SCRIPTS, CHECKLISTS, LOGS, AND SUMMARY TABLES, ETC

ABBR	INSTRUMENT/FORM NAME	VERSIONS	DOMAIN
	General Tracking		
SITE	Site Activity Log		Tracking
ETL	Enrollment Tracking Log		Tracking
STAFF	Site Staff ID Code Log		Tracking
	Screening		
CONSENT	Guardian Consent Form		Consent
ASSENT	Adolescent Assent Form		Consent
PRE	Prescreening Script		Consent
GATEA	Gate A Assessment Checklist		Tracking
GATEB	Gate B Assessment Checklist		Tracking
GATEC	Gate C1 and C2 Assessment Checklist		Tracking
	Assessments		
WK6	Week 6 Assessment Checklist		Tracking
WK12	Week 12 Assessment Checklist		Tracking
WK18	Week 18 Assessment Checklist		Tracking
WK24	Week 24 Assessment Checklist		Tracking
WK30	Week 30 Assessment Checklist		Tracking
WK36	Week 36 Assessment Checklist		Tracking
MN03	Month 03 Assessment Checklist		Tracking
MN06	Month 06 Assessment Checklist		Tracking
MN09	Month 09 Assessment Checklist		Tracking
MN12	Month 12 Assessment Checklist		Tracking
IET	IE Summary Table		Tracking
	Treatment Sessions		
PT-CFA	Pharmacotherapy Checklist for Adherence		Tracking
PTT	Pharmacotherapy Summary Table		Tracking
CBT-CFA	CBT Checklist for Adherence		Tracking
CBTT	CBT Summary Table		Tracking
NOTE	Treatment Note for CBT and PT		Tracking
	Pharmacy		
DAL	Drug Accountability Log *{Return to DCRI Pharmacy}*		Tracking
BDAL	Bulk Drug Accountability Log *{Return to DCRI Pharmacy}*		Tracking

17. Appendix E. Sample Assent/Consent Form for TADS

"Treatment for Adolescents with Depression Study"

PURPOSE

You are being asked to be in a study to help us find out if our treatment is the best way to treat teens like yourself who may be suffering from depression. This study will last about 20 months. Participation is purely voluntary and you do not have to be in the study. You can also change your mind later on without upsetting anyone. Approximately 432 teenagers of either sex, ages 12-17, will be recruited at ten sites in the United States for this study.

PROCEDURES

First, your doctor will determine if you meet the rules to be in the study. This could take up to two half days. Your doctor will talk with you and your parents about yourself and your family, and will ask you to complete some questionnaires. Your doctor will also give you learning tests and a brief physical exam. If you are a girl, you will be asked to give a sample of blood (about one teaspoon) or urine to determine if you are pregnant. You [and your parents, depending on state requirement] and whoever you choose will be told the results of the pregnancy test. If you are pregnant you cannot participate in this study.

If the doctor thinks you meet all the rules for the study and you agree to participate**, y**ou will be assigned to receive one of four treatments. You or the doctor will not be able to decide which treatment you receive. The choice will be based on chance (sort of like flipping a coin) and will be done by a computer. This assigned treatment is planned to last about nine months. The four possible treatments are:

1. Active pill (Prozac) alone
2. Placebo pill ("sugar pill") alone
3. Talking therapy (Cognitive behavior therapy CBT) alone
4. Combination of active pill (Prozac) and CBT

The active pill used in this study is called Prozac. Prozac has been used in the treatment of depression for adults. We are studying how well teenagers do on this medication. You might <u>not</u> receive active medication. You might receive a pill called a placebo that looks like the real medicine, but is not. Neither you nor your doctor will know which type of pill you are taking. There is a one-in-four chance that you will receive placebo.

If you are taking either the active or placebo pill in this study, you will see a medical doctor regularly to see if you need a different dose or if there are any side effects. At first you will see the doctor about every other week, then it will be less if you are doing well. Most visits with the doctor will take about 20 minutes. At the end of 12 weeks (three months), your doctor will be able to find out which treatment you have been given, whether placebo or Prozac, and you will be told. If you have been taking Prozac you will continue to receive Prozac for the remaining six months of the study. If you have been taking placebo and have not gotten better, you will be offered one of the other study treatments of your choice (Prozac, CBT or both).

The talking therapy in this study is called Cognitive Behavior Therapy (CBT). CBT is a therapy that helps you learn new ways to deal with depression. If you are assigned to CBT alone, you will not receive a pill. At first you will have weekly visits with a child psychologist; then the visits will be less frequent if you are doing well. Most CBT visits will take about an hour to 90 minutes. Your parents will attend some visits with you and they will attend some visits alone with the psychologist. CBT continues for nine months.

If you are assigned to the Combination treatment, you will receive both Prozac and CBT. Then you will visit both doctors, one for CBT and one for pills. Combination treatment continue**s** for nine months.

Regardless of which treatment you are receiving, every six weeks you will be asked to fill out more questionnaires like the ones at the beginning of the study and talk with another doctor to see how much you have improved.

Your visits with the study psychologist or study doctor will be audiotaped. These tapes will be listened to by other research staff involved in the study to make sure you are getting good care.

POSSIBLE BENEFITS

It is possible that you will not gain any more benefits from being in this study than you would from getting treatment on your own in your community. However, this study provides a complete evaluation for depression. This information is generally not available with routine care.

All treatments are provided at no charge.

An indirect benefit comes from knowing that the results of this study may help improve the care of other teens with similar problems. It is important that you understand this study is being done so we can learn more about adolescents who are depressed. This study does not promise better or safer treatment than what you could get on your own in the community.

ALTERNATIVE TREATMENTS

Other forms of treatment for depression are available, including other medications and other types of counseling. If you do not wish to participate in this study, your doctor will discuss other treatment options. The treatments that you will receive if you decide to participate in this study may be available in your community and you may be able to receive them even if you do not participate in this study.

RISKS

Sometimes, even with treatment, depression gets worse. It is important that you tell your doctor if you think you are getting worse.

You may become upset or frustrated during interviewing or filling out questionnaires.

You may become upset during CBT, as this is a necessary part of learning how to cope with feelings. However, CBT procedures are designed to minimize difficult feelings. If necessary, extra sessions can be provided by your doctor.

Most persons have few if any side effects from Prozac, but nausea, diarrhea, headache, rash, drowsiness, trouble sleeping, and agitation can occur.

Your doctor may withdraw you from the study if he or she thinks that is in your best interest. If you are withdrawn from the study or do not get better with treatment, your doctors will talk with you about different treatment.

An uncommon but specific side effect of treatment for depression is switching from depression to mania. In contrast to depression, mania is characterized by elevated rather than depressed mood and can be accompanied by more energy, less need for sleep and troublesome activities, such as increased sexual activity or drug use. Your doctor will monitor your mood carefully throughout the study. If mania occurs, you will be withdrawn from the study and will be offered additional interventions outside the study.

For Girls: Since the medication used in this study may not be healthy for an unborn child, you must not be pregnant while in this study. A blood or urine pregnancy test will be done at the beginning of the study to exclude pregnancy. If pregnant, you and whomever you choose [unless otherwise overridden by state law or unacceptable to local IRB] will be told of the results of the pregnancy test and you will not be allowed to be in the study. If sexually active, you must use proven contraceptive measures for the duration of the study. If you become pregnant during the study, you [and your parents] will be told that you must be withdrawn from the medication portion of the study, but may continue with CBT at your option.

You will be told of any changes in the way the study will be done if there are any, and any new risks to which you may be exposed. We will also tell you any new information we learn about depression that may affect your decision to stay in the study.

COMPENSATION

Both the medication and the CBT sessions will be free. There will not be any other charges for the care you receive as part of this study.

You or your parents will receive $10 per regularly scheduled visit to cover travel costs and parking.

Your family also will receive $100 for completing each major assessment visit.

CONFIDENTIALITY OF RECORDS

The information gathered as part of this study will be kept in locked files. In addition to the health care professionals caring for you, your hospital's Institutional Review Board (ethics committee), representatives of Duke University Medical Center, and those assigned by them, and the federal agency sponsoring this trial may need to review your medical records. All information is confidential. However, if we learn that you or someone else is in serious danger of harm (such as in cases of abuse) we may tell others to protect you and/or the other persons. Scientific publications will not mention any patient by name.

PATIENT RIGHTS

Being in this study is entirely voluntary. You are not required to be in this study, even if your parent wishes it. If you decide not to be in this study, the decision not to participate will not influence your medical care at XXXXXX (facility). You can refuse to participate or can withdraw from the study at any time.

OBTAINING ADDITIONAL INFORMATION

You are encouraged to ask questions at any time in the study. You can ask Dr. _____ at ____-_____ or another staff member the next time you are here. Or you may contact an impartial third party, _____, Chairman of the Institutional Review Board, at ____- _____.

STATEMENT OF ASSENT

"I have read the above information or have had it read to me. I have had the opportunity to discuss it and to ask questions. I know that I may contact my doctor to answer any questions. I understand the risks and benefits to participation in the study. I know that I may leave the study at any time. I will get a copy of this consent form when it is signed. I consent to be in this study."

_____ _____

Subject's Signature Date

_____ _____

Signature of Person Explaining and Getting Consent Date

SAMPLE CONSENT FOR TADS

"Treatment for Adolescents with Depression Study"

PURPOSE OF STUDY

You are being asked to allow your teenager to be in a research study funded by the National Institute of Mental Health and coordinated by Duke University Medical Center. Your teenager may be eligible for this study because he or she is depressed and currently requires treatment for depression. Approximately 432 teenagers (between the ages of 12 and 17) will take part in this study at ten sites in the United States.

The purpose of this study is to compare how well different treatments work in teenagers diagnosed with major depressive disorder. A second purpose of this study is to see which treatment(s) produce the most immediate and long-lasting benefit.

YOUR RIGHTS

It is important for you to know:

1. This study is strictly voluntary. No teenager will be required to be in this study, even if his or her parent wishes it.

2. At any time during the course of this study, you or your teenager can change your mind, stop your participation, and receive appropriate treatment elsewhere.

3. If your teenager or you decide not to be in this study, this decision will not affect his or her routine medical care at [facility].

4. You and your teenager will be informed of any changes in the way the study is conducted and any new risks that your teenager may be exposed to, if any should occur. If necessary, you may be asked to sign a new *Informed Consent*.

5. Your teenager and you will be informed of any new information learned during the course of this study that could cause you to stop participating in this study. If it is in your teenager's best interest, your doctor may decide to withdraw him or her from the study without your consent.

STUDY PROCEDURES

Your teenager will first receive a complete diagnostic assessment to determine if he or she is eligible to participate in this study. This assessment will take approximately two half days and will involve interviews with you and your teenager, questionnaires for you and your teenager, an achievement test for your teenager, and a brief physical exam for your teenager. If your teenager is female, she will be asked to give a sample of blood (about one teaspoon) [or urine, depending on site] to determine if she is pregnant. You and your teenager will be told the results of the pregnancy test [include depending on local requirements]. Pregnancy will disqualify your teenager from being in this study.

If your teenager is eligible and you both agree to participate, your teenager will be randomly assigned (meaning assigned by chance, like flipping a coin) to one of four (4) treatment groups. Neither you nor your doctor will be able to decide which treatment your teenager receives; the computer will decide it.

Two of the four treatment groups will receive active (real) medication. The medication used in this study is called fluoxetine, and is more commonly known as Prozac. Research has shown that medications like fluoxetine help depression in young persons. Fluoxetine has been approved by the Food and Drug Administration for use in the treatment of adult depression and is under study for children and teenagers.

One of the two fluoxetine groups will receive only fluoxetine and is referred to as the Fluoxetine alone group. The other group will receive fluoxetine plus Cognitive Behavioral Therapy (CBT) and is referred to as the Combined Fluoxetine and CBT group. CBT is a talking therapy that will teach you and your teenager new skills to cope better with his or her depression. Specific topics include education about depression and the causes of depression, setting goals, monitoring mood, increasing pleasant activities, social problem-solving, correcting negative thinking, negotiation, compromise and assertiveness. CBT sessions will also help with resolving disagreements as they affect your family.

The third treatment group will receive only CBT, without any medication. It is referred to as the CBT alone group.

The fourth treatment group will receive no medication and no CBT. However, those in this group will take a "fake" pill that has been made to look like fluoxetine so that neither the teenager, the parents, nor the doctors will know who is getting real medication and who is not. The group is referred to as the Placebo alone group.

Again, the four possible groups are:

1. Fluoxetine (Prozac) alone
2. Combination of fluoxetine and CBT
3. CBT alone
4. Placebo alone

In groups one and four (Fluoxetine alone and Placebo alone), neither the study doctor nor you will know which medication (i.e., real Prozac or Placebo) your teenager is receiving. However, if it becomes necessary for safety reasons, the study doctor will be able to find out which medicine your teenager has been taking.

The treatment part of this study will be conducted in (3) three stages and may last 36 weeks (9 months), depending on your teenager's response to treatment. A fourth follow-up stage will last one year.

Stage I will last 12-weeks and will compare each of the four treatment groups listed above. Depending on which treatment group your teenager is randomly assigned to, he or she will come to the clinic between 6-12 times during Stage I of the study. If your teenager's depression has worsened or not improved enough during Stage I, the study doctor will talk to you both about other treatment possibilities.

The schedule of visits during Stage I is:

1. If your teenager is assigned to one of the medicine groups (either active medication or "pill placebo"), you and your teenager will visit the study doctor 6 times during Stage I. Each visit should take about thirty minutes. During these visits, the study doctor will ask your teenager about both benefits and side effects before deciding if your teenager needs more of the medicine. As long as your teenager remains depressed, clinic staff will call you to see how he or she is doing during the weeks that you do not see the doctor. At the end of 12 weeks you and your teenager will find out which medication your teen has received.

2. If your teenager is assigned to the CBT alone group, he or she will visit the psychologist during Stage I. There will be approximately 12 CBT sessions, depending on your's and your teen's

need. As a parent, you will attend some sessions, sometimes with your teenager and sometimes alone with the psychologist. Each visit should last one to two hours.

3. If your teenager is assigned to the combination of medication and CBT group, he or she will meet six times with the study doctor (for medication) and about 12 times with the psychologist (for CBT) during Stage I. As a parent, you will also attend some of these visits with your teen and sometimes alone with the psychologist. To minimize the time and trouble to you, these visits will be coordinated back-to-back in the same location.

If your teenager is assigned to the "pill placebo" group and he or she has not improved over the course of Stage I, your teenager will be eligible to receive 12-weeks of the active medicine (fluoxetine) or therapy (CBT) or both, depending on your preference.

Stage II lasts six weeks and is for those teenagers who have responded well during the first 12-weeks of treatment. In Stage II of the study, your teenager's original treatment will be continued and he or she will come to the clinic between 2-6 times during Stage II of the study. If your teenager's depression has worsened or not improved enough during Stage I, the study doctor will talk to you and your teenager about other treatment alternatives.

Stage III lasts 18 weeks, about four months. During Stage III, if your teenager has continued to respond well, he or she will return every six weeks to receive treatment and to monitor progress. If he or she received fluoxetine, he or she will see the doctor who gave the medicine; if she or he received CBT, she or he will see the CBT therapist. If he or she was in the combined group, he or she will see both the CBT therapist and the medication doctor.

At the end of Stage III, your teenager's treatment in this study will end. Your doctor will talk with you and your teenager about the progress your teenager has made and give you recommendations for further treatment and appropriate referrals.

Stage IV lasts one year. During Stage IV, you and your teenager will return every three months for assessments only. Stage IV will help us understand the long-term benefits of the treatments.

By agreeing to be in this study, you also agree to complete <u>all</u> assessment visits even if your teen is no longer receiving treatment from TADS staff. These visits, which are necessary to know how well the treatments work, may or may not be on the same day as a treatment visit.

ASSESSMENTS

There are two kinds of assessment visits, minor and full. <u>Minor</u> assessment visits will take about an hour and will usually happen on the same day as a treatment visit. <u>Full</u> assessment visits will take 3-4 hours and may or may not happen the same day as a treatment visit.

There are five minor and six full assessments over twenty months (Stages I-IV). During Stage I, II and III, an assessment visit will occur every six weeks, with full and minor assessments alternating. Full assessments will occur right before treatment starts and at weeks 12, 24 and 36; minor assessments will occur in-between at weeks 6,18, and 30. During the one year Stage IV follow-up, full and minor assessments will occur every three months, again alternating. Minor assessments will occur at 3 and 9 months after the end of Stage III and full assessments at 6 and 12 months after the end of Stage III.

All of your teenager's treatment visits and some of the assessment visits with the study psychologist or study doctor will be audiotaped or videotaped. The tapes will be listened to by other research staff involved in the study to make sure your teenager is getting good care and to help understand how treatment works. These tapes will be stored for five years after the study is completed after which they will be destroyed. Like all research information, these tapes will be stored in a secure location and will be kept confidential.

BENEFITS

A possible benefit of your teenager's participation in this study is that the treatment may help alleviate his or her symptoms of depression. Your teenager will also receive a thorough evaluation of his or her problem. Such a comprehensive evaluation is generally not available with routine care. Additionally, all treatments are provided at no charge.

An indirect benefit may also come from knowing that the results of this study may help improve the future care of teenagers with similar problems. It is possible, however, that your teenager will not gain any direct benefit from being in this study.

It is important that you understand that this study is being conducted for research purposes and does not ensure better or safer treatment nor guarantee individual benefits to the participant. The contribution made by participating in a clinical trial is to further our knowledge about treating adolescents with depression.

ALTERNATIVE TREATMENTS

If you or your teen do not wish to participate, your doctor will discuss other treatment options. The treatments that your teen will receive by participating in this study are available in your community and your teen may be able to receive them without participating in this study. It is possible that you may not receive any better care in this study than you could receive in your community.

RISKS

Teenagers sometimes become upset or frustrated during psychiatric interviewing or filling out questionnaires. However, each of the measures chosen for this study has been used extensively with hundreds of teenagers without ill effects.

Teenagers may also experience mild distress during CBT, as this is a necessary part of learning how to cope more effectively with feelings. However, this risk is minimal as CBT procedures are designed in general to lessen distress. If necessary, the study doctor will provide up to four (4) additional individual problem-solving sessions to help any teenager that may experience excessive distress during the course of this study.

Most teenagers have few if any side effects from fluoxetine, but nausea, diarrhea, headache, rash, drowsiness, trouble sleeping, and agitation can occur. If a teenager shows unusually high levels of distress or side effects from medication, or requires more than four (4) additional sessions to manage side effects, the doctor may withdraw him or her from the study.

Some teenagers in this study will receive an inactive medication ("sugar pill") during the first stage of the study. Sometimes a person will get better by taking a placebo pill, but there is a higher chance that your teenager will not receive any benefit. There is also a chance that your teenager's symptoms will worsen. For example, your teenager may experience symptoms of low mood, sleep or appetite disturbance, low energy or interest, or suicidal feelings. Throughout the study, the treatment team will frequently monitor your teenager's progress to see if his or her symptoms are worsening. It is important to notify the research team if your teenager looks like he or she is getting worse.

An uncommon but specific side effect of medication treatment for depression is switching from depression to mania. In contrast to depression, which is characterized by sad or low mood and no energy, mania is characterized by high rather than depressed mood and can be accompanied by more energy, becoming very "hyper", super happy, silly or cranky, becoming more talkative, feeling pressured to keep talking, feeling that thoughts are racing, having big ideas, having less need for sleep, feeling overconfident and becoming involved in risky and troublesome activities, such as increased sexual activity or drug use. Your doctor will monitor your teen's mood carefully throughout the study. If mania occurs, he or she will be withdrawn from the study and will be referred for additional

interventions outside the study.

Since the medication used in this study may not be healthy for an unborn child, your teen must not be pregnant while in this study. A blood [or urine, depending on site] pregnancy test will be done at the beginning of the study to exclude pregnancy. If pregnant, your teenager and whomever she chooses will be told the results of this test [this clause added depending on state law]and your teen will not be allowed to be in the study. If sexually active, your teen must use proven contraceptive measures for the duration of the study. If she becomes pregnant during the study, your teen will be withdrawn from the medication portion of the study, but may continue with CBT at your teenager's option.

Teenagers who do not improve during Stage I of the study or who relapse at any time will be referred to other mental health providers experienced in the treatment of depression for teenagers. If other treatments (i.e., family therapy, or other medications) are necessary, you or your health insurance company will be responsible for paying for these services.

COMPENSATION

There will be no cost to you or your teenager for being in this study. Medication and visits with the study doctors will be free. You will receive $10 dollars per regularly scheduled visit to cover travel and parking costs. Additionally, you will receive $100 for each assessment visit that is completed. Costs for medical care that is not part of this study will be charged to your health insurance.

CONFIDENTIALITY OF RECORDS

The information gathered as part of this study will be kept in a locked room and/or in a locked file cabinet. In addition to the health care professionals caring for your teenager, the Institutional Review Board (ethics committee) at [site], representatives of Duke University Medical Center and those assigned by them, and the federal agency sponsoring this study may need to review your teenager's medical records At the end of the study, the information will be analyzed using only codes and not names. Scientific publications will not mention your teenager by name.

The researchers have obtained a Certificate of Confidentiality from the Federal Government that will help them protect your privacy, unless you consent in writing to the release of research information. This certificate helps protect your and your teenager's privacy and helps the researchers protect information in your records from being legally accessed for civil or criminal actions, even if the records are sought by the courts or other authorities without your permission. However, if they learn that you or someone else is in serious danger of harm [such as in cases of abuse] they may make disclosures to protect you and/or the other persons.

The research team is required to report certain circumstances such as ongoing child abuse, suicidal or homicidal ideas or intent to authorities. Your teenager's records may be made available to them, even without your consent.

RESEARCH-RELATED INJURY

In the unlikely event your teenager is injured as a direct result of taking part in this study, emergency psychiatric treatment will be made available primarily through [site]. In addition, you will be given help in arranging follow-up care for your teenager. However, the cost for this treatment will be charged to you or to your health insurance. This study does not provide compensation or payment for this follow-up treatment.

OBTAINING ADDITIONAL INFORMATION

You and your teenager are encouraged to ask questions at any time during this study. If you have further questions about the study, you can call Dr. [Principal Investigator] at [phone number]. Or you may contact an impartial third party, [name], Chairman of the Institutional Review Board, at [phone number]. You may also contact the Institutional Review Board regarding questions concerning your teenager's

rights as a research subject.

STATEMENT OF ASSENT

"I have read the above information or it has been read to me. I have had the opportunity to discuss it and to ask questions. I have been informed that I may contact _____or my doctor to answer any questions I may have during this study. I understand the risks and benefits of participating in the study. I know that leaving the study at any time is allowed and will not interfere with my regular care. I will get a copy of this consent form when it is signed. I voluntarily agree to be in this study."

_____ _____

Subject's Signature Date

STATEMENT OF PERMISSION

"I have read the above information or it has been read to me. I have had the opportunity to discuss it and to ask questions. I have been informed that I may contact _____or my doctor to answer any questions I may have during this study. I understand the risks and benefits of my teenager's participation in the study. I know that leaving the study at any time is allowed and will not interfere with my teenager's regular care. I will get a copy of this consent form when it is signed. I agree to allow my teenager to be in this study"

_____ _____

Signature of Parent or Legal Guardian Date

_____ _____

Signature of Person Explaining and Getting Consent Date