University of Minnesota

A PERSONALIZED APPROACH TO ACHIEVING A SUSTAINED RESPONSE TO TREATMENT FOR ADOLESCENT DEPRESSION

Phase II, pilot study, open trial

Regulatory Sponsor:	*Meredith Gunlicks-Stoessel* *Department of Psychiatry* *University of Minnesota*
Funding Sponsor:	*Minnesota Medical Foundation (MMF), University of Minnesota Office of the Vice President for Research*
Study Product:	*Interpersonal Psychotherapy for Depressed Adolescents (IPT-A) and Prozac (Fluoxetine)*
Protocol Number:	*N/A*
UMN IRB code:	*1206M15365*

Date updated: 7-6-15

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List of Abbreviations

AE	Adverse Event
CC	Cubic Centimeters
CDRS	Children's Depression Rating Scale
CFR	Code of Federal Regulations
CGI	Clinical Global Impressions
CMRR	Center for Magnetic Resonance Research
CRF	Case Report Form
CTSI	Clinical and Translational Science Institute
DSMB	Data and Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
IDS	Investigational Drug Services
IRB	Institutional Review Board
KG	Kilogram
K-SADS-PL	Kiddie-Sads-Present and Lifetime
MDD	Major-Depressive Disorder
MEG	Magnetoencephalography
MG	Milligram
ML	Milliliter
MMC	Mayo Mail Code
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NOS	Not Otherwise Specified
PET	Positron Emission Tomography
PHA	Phytohemagglutinin
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event
TRD	Treatment-Resistant Depression
VA	Veterans' Affairs

Information Resources

	Name / Address	Phone / Fax / E-mail
Principal Investigator	Meredith Gunlicks-Stoessel 2450 Riverside Ave Minneapolis, MN 55454	612-273-9844 mgunlick@umn.edu
Questions concerning eligibility	Ana Westervelt 2450 Riverside Ave Minneapolis, MN 55454	612-626-7065 Bortn005@umn.edu
For patient enrollment	Ana Westervelt	
Questions concerning drug ordering, Shipment, transfer or returns	Ana Westervelt	
Lab shipping or requests	Ana Westervelt	
Submission of data forms / Questions on data management	Ana Westervelt	

Study Summary

Title	*A Personalized Approach to Achieving a Sustained Response to Treatment for Adolescent Depression*
Short Title	*PTAD GIA*
Protocol Number	*1206M15365*
Phase	*2*
Methodology	*open label pilot*
Study Duration	*3 years*
Study Center(s)	*Single-center*
Objectives	*To develop and assess the feasibility, acceptability, and preliminary efficacy of a personalized approach to delivering continuation treatment*
Number of Subjects	*30*
Diagnosis and Main Inclusion Criteria	*Male and female adolescents (ages 12-18) will be eligible for the study if they completed acute phase treatment and showed at least a partial response to treatment (CGI-I of minimally improved or better (CGI-I ≤ 3)). Adolescents will enter continuation treatment having either received 12 sessions of IPT-A, 16 sessions of IPT-A, or 12 sessions of IPT-A plus fluoxetine.*
Study Product, Dose, Route, Regimen	*Adolescents who received fluoxetine during the acute phase and were responders (CGI-I = much improved or very much improved* (CGI-I = 1 or 2)*) will continue their acute phase dosing regimen and will meet with the psychiatrist on a monthly basis. Adolescents who received fluoxetine during the acute phase and were partial responders (CGI-I = minimally improved* (CGI-I = 3)*) will enter the continuation phase on 40mg fluoxetine, and will have their dose increased to 60mg. Adolescents who received only IPT-A during acute phase and were partial responders (CGI-I = minimally improved* (CGI-I = 3)*) will begin treatment with fluoxetine, in addition to continuing their IPT-A treatment. The dosage schedule will be 10mg per day for the first week and 20mg per day for the following 5 weeks. If no treatment response is observed by the 6th week, the dosage can be increased to 40mg per day.15*
Duration of administration	*16 weeks*
Reference therapy	*Interpersonal Psychotherapy for Depressed Adolescents (IPT-A)*

Statistical Methodology	*1. Mean [95% confidence interval] treatment satisfaction for each adaptive treatment strategy (ATS)* *2. Mean therapy session attendance and dropout rates for each ATS.* *3.* Within-subject change scores in CDRS-R, SAS-SR, and CGAS scores for the early and late decision point groups from pre- to post-treatment using repeated measures ANOVA.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 or 812 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Adolescent depression is a prevalent and debilitating disorder that places youth at risk for suicidality, other psychiatric diagnoses, and significant psychosocial impairment both during adolescence and into adulthood.[1,2] Research on the treatment of adolescent depression has dramatically increased over the past two decades. Two psychotherapies meet the American Psychological Association's criteria for "well-established" treatments (interpersonal psychotherapy and cognitive behavioral therapy).[3] Fluoxetine, paroxetine, sertraline, and escitalopram also have demonstrated efficacy as pharmacological treatments.[4-8] While the progress in this area has been substantial, the overwhelming majority of treatment studies have focused on the acute phase of treatment, that is, the phase of treatment focused on initial clinical response and remission of symptoms.[9] However, among the acute treatment studies that have reported long-term follow-up data, 25-50% of the adolescents in these studies experienced a depressive relapse following the completion of treatment.[10-13]

The American Academy of Child and Adolescent Psychiatry Practice Parameter for the treatment of depression recommends providing continuation treatment following the symptom remission achieved during the acute phase of treatment.[14] The goals of continuation treatment are to consolidate the acute phase treatment response and avoid relapse. Research on continuation phase treatment for adolescent depression is extremely limited, and as a consequence, this Practice Parameter was based primarily on adult treatment studies and clinical consensus.[14] The handful of studies with adolescents that have examined postacute treatment have found that continuation treatment is associated with a decreased risk of relapse,[11,15,16] and can facilitate further symptom reduction in adolescents who were partial responders to acute phase treatment.[11,17]

One of the primary risk factors for relapse in youth is interpersonal conflict, particularly within the adolescent's family.[10,18] As a consequence, it has been recommended that continuation treatments for adolescent depression focus not only on the depressive symptoms, but on the family conflict and relationship problems that may trigger a relapse.[19] Interpersonal Psychotherapy for Depressed Adolescents (IPT-A)[20] is a natural treatment modality for targeting both depressive symptoms and interpersonal risk factors. IPT-A is an evidence-based psychotherapy that aims to reduce adolescents' depressive symptoms by helping them improve their relationships and interpersonal interactions.[21-23] Of note, our group found that the benefits of IPT-A are particularly strong for adolescents who report high levels of conflict with their mothers.[24] This finding is significant in light of previous studies that have found that perceived parent–adolescent conflict predicted a poorer treatment response.[10,25] A continuation

version of IPT-A has not yet been studied in a clinical trial. However, IPT as a continuation treatment for adult depression has been investigated, and the results indicated that patients had significantly lower relapse rates.[26,27] In addition, continuation IPT has been found to decrease the impact of negative life events in provoking relapse.[28] This suggests that continuation versions of IPT-A may be useful for preventing the relapse of adolescent depression, as well.

The primary aim of this study is to develop and assess the feasibility and acceptability of a personalized approach to delivering continuation treatment for adolescent depression. The development of evidence-based guidelines for personalizing treatments has been identified as a public health priority[29] (NIMH Strategic Plan, 2008, Strategy 3.2: Expand and deepen the focus to personalize intervention research). Personalized interventions, also known as adaptive treatment strategies, provide empirically-derived guidelines or decision rules that recommend when, how, and for whom treatment should be changed to meet the needs of individual patients.[30,31] Adaptive treatment strategies can, for example, operationalize for patients who are responding to a given treatment, what kind of treatment plan to follow for the continuation phase of treatment. These decision rules are based on patient characteristics and outcomes collected during the treatment process, such as patient response and adherence.

We are currently conducting a pilot study of a personalized approach to acute phase treatment for adolescent depression (Gunlicks-Stoessel, PI, K23MH090216). Adolescents begin treatment with IPT-A and may have their treatment augmented either with an increased number of therapy sessions or the addition of fluoxetine if they are showing an insufficient response to treatment. The proposed study would examine the feasibility and acceptability of extending the adaptive treatment strategy into the continuation phase of treatment. There is a clear need for the development and empirical examination of continuation treatments for depression in youth. Given the significant impact that adolescent depression has on both adolescent and adult development and functioning, a continuation treatment that achieves a sustained remission and prevents relapse could have considerable public health significance.

1.2 Investigational Agent

PROZAC® (fluoxetine capsules, USP) is a selective serotonin reuptake inhibitor for oral administration. It is also marketed for the treatment of premenstrual dysphoric disorder (Sarafem®, fluoxetine hydrochloride). It is designated (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride and has the empirical formula of C17H18F3NO•HCl. Its molecular weight is 345.79.

Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water. Each Pulvule® contains fluoxetine hydrochloride equivalent to 10 mg (32.3 µmol), 20 mg (64.7 µmol), or 40 mg (129.3 µmol) of fluoxetine. The Pulvules also contain starch, gelatin, silicone, titanium dioxide, iron oxide, and other inactive ingredients. The 10 and 20 mg Pulvules also contain FD&C Blue No. 1, and the 40 mg Pulvule also contains FD&C Blue No. 1 and FD&C Yellow No. 6.

PROZAC Weekly™ capsules, a delayed-release formulation, contain enteric-coated pellets of fluoxetine hydrochloride equivalent to 90 mg (291 µmol) of fluoxetine. The capsules also contain D&C Yellow No. 10, FD&C Blue No. 2, gelatin, hypromellose, hypromellose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, triethyl citrate, and other inactive ingredients.

Although the exact mechanism of PROZAC is unknown, it is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Studies at clinically relevant doses in man have demonstrated that fluoxetine blocks the uptake of serotonin into human platelets. Studies in animals also suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of norepinephrine. Antagonism of muscarinic, histaminergic, and α1-adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects of classical tricyclic antidepressant (TCA) drugs. Fluoxetine binds to these and other membrane receptors from brain tissue much less potently in vitro than do the tricyclic drugs.

Systemic Bioavailability — In man, following a single oral 40 mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours. The Pulvule and PROZAC Weekly capsule dosage forms of fluoxetine are bioequivalent. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant. Thus, fluoxetine may be administered with or without food. PROZAC Weekly capsules, a delayed-release formulation, contain enteric-coated pellets that resist dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. The enteric coating delays the onset of absorption of fluoxetine 1 to 2 hours relative to the immediate-release formulations. OCHCH2CH2NHCH3• HClF3C21

Weekly Dosing — Administration of PROZAC Weekly once weekly results in increased fluctuation between peak and trough concentrations of fluoxetine and norfluoxetine compared with once-daily dosing [for fluoxetine: 24% (daily) to 164% (weekly) and for norfluoxetine: 17% (daily) to 43% (weekly)]. Plasma concentrations may not necessarily be predictive of clinical response. Peak concentrations from once-weekly doses of PROZAC Weekly capsules of fluoxetine are in the range of the average concentration for 20 mg once-daily dosing. Average trough concentrations are 76% lower for fluoxetine and 47% lower for norfluoxetine than the concentrations maintained by 20 mg once-daily dosing. Average steady-state concentrations of either once-daily or once-weekly dosing are in relative proportion to the total dose administered. Average steady-state fluoxetine concentrations are approximately 50% lower following the once-weekly regimen compared with the once-daily regimen. Cmax for fluoxetine following the 90 mg dose was approximately 1.7-fold higher than the Cmax value for the established 20 mg once-daily regimen following transition the next day to the once-weekly regimen. In contrast, when the first 90 mg once-weekly dose and the last 20 mg once-daily dose were separated by 1 week, Cmax values were similar. Also, there was a transient increase in the average steady-state concentrations of fluoxetine observed following transition the next day to the once-weekly regimen. From a pharmacokinetic

perspective, it may be better to separate the first 90 mg weekly dose and the last 20 mg once-daily dose by 1 week [see Dosage and Administration (2.1)].

Daily Dosing -- Adult — The efficacy of PROZAC was studied in 5- and 6-week placebo-controlled trials with depressed adult and geriatric outpatients (≥18 years of age) whose diagnoses corresponded most closely to the DSM-III (currently DSM-IV) category of Major Depressive Disorder. PROZAC was shown to be significantly more effective than placebo as measured by the Hamilton Depression Rating Scale (HAM-D). PROZAC was also significantly more effective than placebo on the HAM-D subscores for depressed mood, sleep disturbance, and the anxiety subfactor.

Two 6-week controlled studies (N=671, randomized) comparing PROZAC 20 mg and placebo have shown PROZAC 20 mg daily to be effective in the treatment of elderly patients (≥60 years of age) with Major Depressive Disorder. In these studies, PROZAC produced a significantly higher rate of response and remission as defined, respectively, by a 50% decrease in the HAM-D score and a total endpoint HAM-D score of ≤8. PROZAC was well tolerated and the rate of treatment discontinuations due to adverse reactions did not differ between PROZAC (12%) and placebo (9%).

A study was conducted involving depressed outpatients who had responded (modified HAMD-17 score of ≤7 during each of the last 3 weeks of open-label treatment and absence of Major Depressive Disorder by DSM-III-R criteria) by the end of an initial 12-week open-treatment phase on PROZAC 20 mg/day. These patients (N=298) were randomized to continuation on double-blind 23 PROZAC 20 mg/day or placebo. At 38 weeks (50 weeks total), a statistically significantly lower relapse rate (defined as symptoms sufficient to meet a diagnosis of Major Depressive Disorder for 2 weeks or a modified HAMD-17 score of ≥14 for 3 weeks) was observed for patients taking PROZAC compared with those on placebo.

Pediatric (children and adolescents) — The efficacy of PROZAC 20 mg/day in children and adolescents (N=315 randomized; 170 children ages 8 to <13, 145 adolescents ages 13 to ≤18) was studied in two 8- to 9-week placebo-controlled clinical trials in depressed outpatients whose diagnoses corresponded most closely to the DSM-III-R or DSM-IV category of Major Depressive Disorder.

In both studies independently, PROZAC produced a statistically significantly greater mean change on the Childhood Depression Rating Scale-Revised (CDRS-R) total score from baseline to endpoint than did placebo. Subgroup analyses on the CDRS-R total score did not suggest any differential responsiveness on the basis of age or gender.

Weekly dosing for Maintenance/Continuation Treatment--A longer-term study was conducted involving adult outpatients meeting DSM-IV criteria for Major Depressive Disorder who had responded (defined as having a modified HAMD-17 score of ≤9, a CGI-Severity rating of ≤2, and no longer meeting criteria for Major Depressive Disorder) for 3 consecutive weeks at the end of 13 weeks of open-label treatment with PROZAC 20 mg once daily. These patients were randomized to double-blind, once-weekly continuation treatment with PROZAC Weekly, PROZAC 20 mg once daily, or placebo.

PROZAC Weekly once weekly and PROZAC 20 mg once daily demonstrated superior efficacy (having a significantly longer time to relapse of depressive symptoms) compared with placebo for a period of 25 weeks. However, the equivalence of these 2 treatments during continuation therapy has not been established.

---------- INDICATIONS AND USAGE ----------

PROZAC® (fluoxetine hydrochloride) is a selective serotonin reuptake inhibitor indicated for:

- Acute and maintenance treatment of Major Depressive Disorder (MDD) in adult and pediatric patients aged 8 to 18 years
- Acute and maintenance treatment of Obsessive Compulsive Disorder (OCD) in adult and pediatric patients aged 7 to 17 years
- Acute and maintenance treatment of Bulimia Nervosa in adult patients
- Acute treatment of Panic Disorder, with or without agoraphobia, in adult patients

---------- DOSAGE AND ADMINISTRATION ---------- Indication	**Adult**	**Pediatric**
MDD (2.1)	20 mg/day in am (initial dose)	10 to 20 mg/day (initial dose)
Depressive Episodes Associated with Bipolar I Disorder (2.5)	Oral in combination with olanzapine: 5 mg of oral olanzapine and 20 mg of fluoxetine once daily (initial dose)	-
Treatment Resistant Depression (2.6)	Oral in combination with olanzapine: 5 mg of oral olanzapine and 20 mg of fluoxetine once daily (initial dose)	-

---------- DOSAGE FORMS AND STRENGTHS ----------

• Pulvules: 10 mg, 20 mg, 40 mg (3)
• Weekly capsules: 90 mg (3)

1.3 Clinical Data to Date

Psychotherapy. According to the American Psychological Association's criteria for evaluating the extent to which a particular psychosocial intervention model has evidence of treatment efficacy to warrant its dissemination,[32,33] interpersonal psychotherapy (IPT-A) has been categorized as a "well-established" intervention for adolescent depression.[3] In clinical trials, depressed adolescents treated with IPT-A demonstrated fewer depressive symptoms, better social functioning, and better global functioning at the completion of treatment than adolescents in control conditions. [21-23]

Pharmacotherapy. Fluoxetine has a treatment response rate of approximately 60% [4,13,34,35]. It is one of two antidepressant medications that has FDA approval for use with children and adolescents.

Combined Treatment. Five recent studies have examined the efficacy of a combination of psychotherapy and medication in comparison to psychotherapy alone and/or medication alone, with response rates ranging from 50-70%.[35-39] Three studies found that the combined treatment approach was significantly more efficacious in reducing depressive symptoms than medication or psychotherapy alone,[35-37] whereas the other two did not.[38,39]

1.4 Dose Rationale and Risk/Benefits

Adolescents who received fluoxetine during the acute phase and were responders (CGI-I = much improved or very much improved) will continue their acute phase dosing regimen and will meet with the psychiatrist on a monthly basis. Adolescents who received fluoxetine during the acute phase and were partial responders (CGI-I = minimally improved) will enter the continuation phase on 40mg fluoxetine, and will have their dose increased to 60mg.[40] Partial responders will meet with the psychiatrist biweekly for the first 2 months and monthly for the second 2 months. Adolescents who received only IPT-A during acute phase and were partial responders (CGI-I = minimally improved) will begin treatment with fluoxetine during the continuation phase, in addition to continuing their IPT-A treatment. The dosage schedule will be 10mg per day for the first week and 20mg per day for the following 5 weeks. If no treatment response is observed by the 6th week, the dosage can be increased to 40mg per day.[41] Pharmacotherapy sessions will be scheduled weekly for the first 4 weeks and biweekly thereafter. Pharmacotherapy sessions will include assessment of vital signs, adverse effects, safety, and symptomatic response.

The major risks of this study are deterioration with study treatment or the experience of side effects with fluoxetine, if prescribed. The benefits to the subjects are having extensive psychiatric assessments and a possible reduction in depressive symptoms and improvement in social and family functioning with study treatment. The treatments provided in this study are empirically-supported treatments for adolescent depression. Many community clinicians are not trained in evidence-based treatments, and so it is

possible that adolescents seeking treatment from a community clinic might be at a greater risk for clinical deterioration and might be less likely to demonstrate a clinical improvement than if they received the treatments provided in this study. What is experimental in this study is the criteria for initiating a change in the treatment plan, the timing of a potential change in the treatment plan, and the type of change to the treatment plan. Currently, there are virtually no empirically-derived guidelines to direct clinicians in deciding whether, when, or how to alter a treatment plan for adolescent depression. Consequently, we expect the relation of the anticipated benefits to the risks to be at least as favorable to the subjects as that presented by available non-study treatment.

2 Study Objectives

Aim 1: Assess the feasibility and acceptability of the personalized continuation treatment strategy.

- Hypothesis 1: Adolescents who responded to the acute phase treatment provided in the K23 study and their parents will consent to participate in continuation treatment.
- Hypothesis 2: Adolescents will be adherent to continuation treatment and will complete the continuation treatment protocol.
- Hypothesis 3: Adolescents and parents will report satisfaction with continuation treatment.
- Hypothesis 4: Treating clinicians will report satisfaction with continuation treatment.

Aim 2: Estimate variances of primary and secondary outcomes with the continuation treatment.

- Hypothesis 5: Adolescents who were responders to acute treatment will show sustained response to continuation treatment.
- Hypothesis 6: Adolescents who were partial responders to acute treatment will show significant improvement in depressive symptoms and social and global functioning.

Aim 3: Conduct exploratory hypothesis-generating analyses to inform further development of the personalized continuation treatment strategy to be tested in a subsequent R01 proposal.

3 Study Design

3.1 General Design

Adolescents will receive 16 weeks of continuation treatment. They will be treated by the same clinicians who provided their acute phase treatment. The personalized continuation treatment plan is illustrated below.

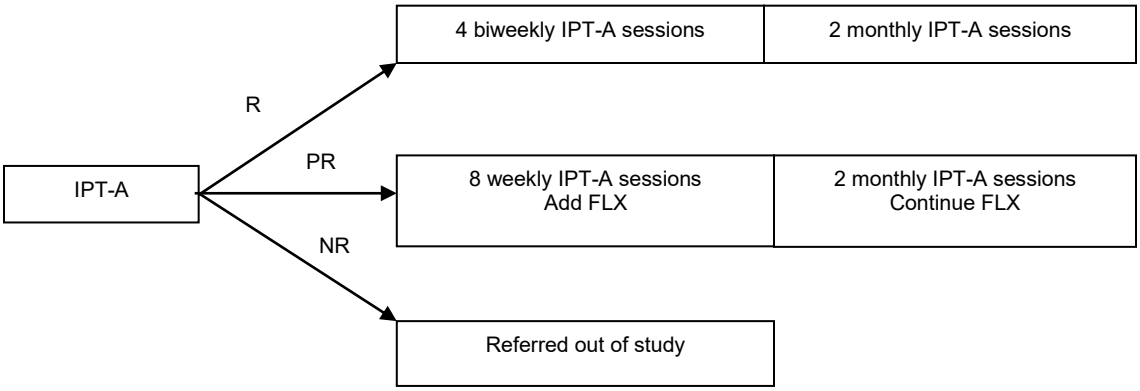
Continuation IPT-A. The goal of IPT-A[20] is to decrease depressive symptoms by focusing on current interpersonal difficulties and helping the individual improve his or her relationships and interpersonal interactions. This is accomplished through review of the

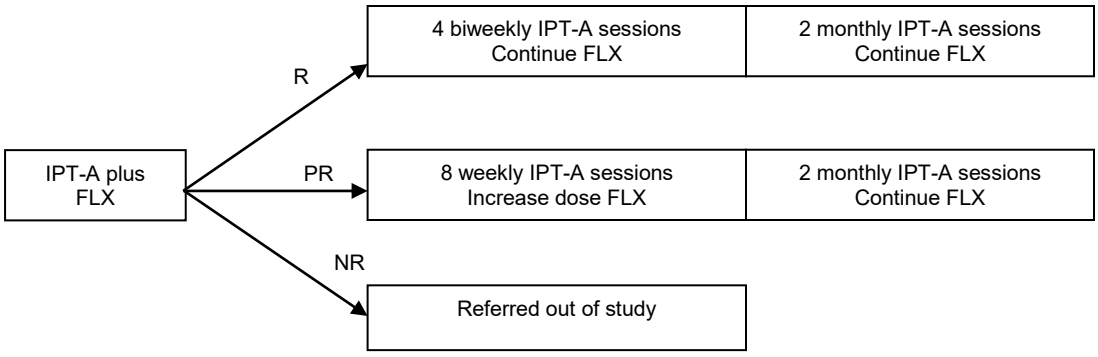
adolescent's significant relationships which leads to the identification of the interpersonal problem areas on which to focus the treatment, development of communication and interpersonal problem solving skills, and role-playing. During the Continuation IPT-A sessions, the therapist will continue to emphasize the interpersonal strategies that were learned and practiced during the acute phase, and address any current interpersonal problems before they result in a recurrence of depressive symptoms. Adolescents who have responded to acute phase treatment (CGI-I = much improved or very much improved) will attend 4 biweekly IPT-A sessions followed by 2 monthly sessions. Adolescents who showed a partial response to acute phase treatment (CGI-I = minimally improved) will attend 8 weekly IPT-A sessions followed by 2 monthly sessions.

Continuation Pharmacotherapy. Adolescents who received fluoxetine during the acute phase and were responders (CGI-I = much improved or very much improved) will continue their acute phase dosing regimen and will meet with the psychiatrist on a monthly basis. Adolescents who received fluoxetine during the acute phase and were partial responders (CGI-I = minimally improved) will enter the continuation phase on 40mg fluoxetine, and will have their dose increased to 60mg.[40] Partial responders will meet with the psychiatrist biweekly for the first 2 months and monthly for the second 2 months. Adolescents who received only IPT-A during acute phase and were partial responders (CGI-I = minimally improved) will begin treatment with fluoxetine during the continuation phase, in addition to continuing their IPT-A treatment. The dosage schedule will be 10mg per day for the first week and 20mg per day for the following 5 weeks. If no treatment response is observed by the 6th week, the dosage can be increased to 40mg per day.[41] Pharmacotherapy sessions will be scheduled weekly for the first 4 weeks and biweekly thereafter. Pharmacotherapy sessions will include assessment of vital signs, adverse effects, safety, and symptomatic response.

Assessments. Assessments will be administered by independent evaluators who are blind to treatment condition. Adolescents will enter continuation treatment at week 16. Assessments will be conducted at week 24 and 32. The week 32 evaluation is already funded through the K23 study. Assessment measures include the Schedule for Affective Disorders and Schizophrenia for School-aged Children-Present and Lifetime Version (K-SADS-PL),[42] Children's Depression Rating Scale-Revised (CDRS-R),[43] Columbia Suicide Severity Rating Scale (CSSRS),[44] Global Assessment Scale for Children (C-GAS),[45] Beck Depression Inventory-II (BDI-II),[46] Social Adjustment Scale-Self-report (SAS-SR),[47] Conflict Behavior Questionnaire (CBQ),[48] and Client Satisfaction Questionnaire (CSQ-8).[49]

Treatment Phase	Acute	Continuation	
Assessment	Week 16	Week 24	Week 32





R = Responder (CGI-I = much improved or very much improved), PR = Partial Responder (CGI-I = minimally improved),
NR = Nonresponder (CGI-I = no change or worsening)

3.2 Primary Study Endpoints

The primary outcome measure is feasibility/acceptability (treatment satisfaction, session attendance, drop-out rates)

3.3 Secondary Study Endpoints

The secondary outcome measures include depressive symptoms Children's Depression Rating Scale (CDRS), Children's Global Assessment Scale (C-GAS), Social Adjustment Scale (SAS-SR), and response status as defined by Clinical Global Impressions Scale (CGI).[50] Responders will be defined as having a 1 or 2 (much or very much improved), partial responders will be defined as having a 3 (minimally improved) whereas non-responders will be defined as having a 4-7 on the CGI (minimally improved to very much worse).

3.4 Primary Safety Endpoints

Primary safety endpoints include suicidality (Columbia Suicide Severity Rating Scale), side effects (Side Effects Measure), and vital signs (blood pressure, pulse, weight).

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

- Male and female adolescents ages 12-18
- Completed acute phase treatment and showed at least a partial response to treatment (CGI-I of minimally improved or better *(CGI-I $\leq$ 3)*).[50]

4.2 Exclusion Criteria

- Completed acute phase treatment and were are non-responder to treatment (CGI-I of no change or worsening *(CGI-I $\geq$ 4)*).

4.3 Subject Recruitment and Screening

We will only enroll adolescents who completed acute phase treatment in our linked study (Gunlicks-Stoessel, PI, K23MH090216) and showed at least a partial response to treatment (CGI-I of minimally improved or better (CGI-I $\leq$ 3)). Adolescents will enter continuation treatment having either received 12 sessions of IPT-A, 16 sessions of IPT-A, or 12 sessions of IPT-A plus fluoxetine.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

A subject may be withdrawn from the study prior to expected completion for the following reasons:

- Participant or participant's parent(s) withdraw consent
- Participant fails to adhere to protocol requirements (no show to 3 appointments)

- Participant experiences adverse side effects to the fluoxetine that are intolerable to the adolescent or the parent.
- Participant experiences a significant worsening in symptoms: the participant will be evaluated by an independent safety monitor if at any time any of the following occur: 1) a suicide attempt, 2) serious suicidal ideation (with a plan and/or intent) and refusal to contract for safety, 3) psychiatric hospitalization, 4) possible need for psychiatric hospitalization, or 5) significant worsening of depressive or other clinical symptoms (CDRS-R> 76 or CGI improvement score> 5). Adolescents will be removed from the study immediately following review if the independent safety monitor deems that the patient requires treatment outside of study protocols or if the treatment provided in the study is contraindicated.

If a subject exits the study for any reason, the participant will be provided with referrals to receive treatment out of the protocol.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

In the event of subject withdrawal from the treatment, we will ask permission to contact the family to continue to complete the study evaluations. Subjects will be determined lost to follow-up if they do not respond to 3 phone calls to their primary number.

5 Study Drug

5.1 Description

The study drug will come as a tablet that the participant will be advised to take once a day, preferably in the morning with a meal.

5.2 Treatment Regimen

Adolescents who received fluoxetine during the acute phase and were responders (CGI-I = much improved or very much improved (CGI-I = 1 or 2)) will continue their acute phase dosing regimen and will meet with the psychiatrist on a monthly basis. Adolescents who received fluoxetine during the acute phase and were partial responders (CGI-I = minimally improved (CGI-I = 3)) will enter the continuation phase on 40mg fluoxetine, and will have their dose increased to 60mg. Partial responders will meet with the psychiatrist biweekly for the first 2 months and monthly for the second 2 months. Adolescents who received only IPT-A during acute phase and were partial responders (CGI-I = minimally improved (CGI-I = 3)) will begin treatment with fluoxetine during the continuation phase, in addition to continuing their IPT-A treatment. The dosage schedule will be 10mg per day for the first week and 20mg per day for the following 5 weeks. If no treatment response is observed by the 6th week, the dosage can be increased to 40mg per day. Pharmacotherapy sessions will be scheduled weekly for the first 4 weeks and biweekly thereafter. Pharmacotherapy sessions will include assessment of vital signs, adverse effects, safety, and symptomatic response.

5.3 Method for Assigning Subjects to Treatment Groups

There is no randomization in this study. Assignment to treatment groups is described above (based on CGI-I score).

5.4 Preparation and Administration of Study Drug

The study psychiatrist will give the adolescent a prescription for the study medication that they will then fill with a licensed pharmacy.

5.5 Subject Compliance Monitoring

Adolescents will be given enough pills to last until their next scheduled appointment and will be asked to bring back the bottle of pills to each appointment. The study coordinator or the psychiatrist will count the number of pills remaining to assess treatment adherence. Families will be provided with the study pager number with instructions for emergencies during after hours. Families will be advised to call 911 in case of life threatening emergencies.

5.6 Prior and Concomitant Therapy

Adolescents will not be permitted to take any medications for a psychiatric diagnosis other than ADHD. Depressed adolescents with a comorbid diagnosis of ADHD who are on a stable dose of stimulant medication (> 3 months) will be eligible to participate in the studies. Adolescents will not be permitted to participate in alternative forms of psychotherapy (e.g. family therapy, group therapy, additional individual therapy).

5.7 Drug Supply

The psychiatrist will give the adolescent a prescription for the study medication that they will then fill with a licensed pharmacy. If the families' insurance company does will not cover the cost of the medication, the family will need to pay for the medication out of pocket.

The following products are manufactured by Eli Lilly and Company for Dista Products Company: Pulvule are available in 10mg, 20mg and 40mg capsule strengths and packages as follows:

Pulvule Strength			
	10 mg1	**20 mg1**	**40 mg1**
Pulvule No.2	PU3104	PU3105	PU3107
Cap Color	Opaque green	Opaque green	Opaque green
Body Color	Opaque green	Opaque yellow	Opaque orange
Identification	DISTA 3104 Prozac 10 mg	DISTA 3105 Prozac 20 mg	DISTA 3107 Prozac 40 mg

6 Study Procedures

Continuation IPT-A. Adolescents who have responded to acute phase treatment (CGI-I = much improved or very much improved) will attend 4 biweekly IPT-A sessions followed by 2 monthly sessions. Adolescents who showed a partial response to acute phase treatment (CGI-I = minimally improved) will attend 8 weekly IPT-A sessions followed by 2 monthly sessions.

Continuation Pharmacotherapy. Adolescents who received fluoxetine during the acute phase and were responders (CGI-I = much improved or very much improved) will continue their acute phase dosing regimen and will meet with the psychiatrist on a monthly basis. Adolescents who received fluoxetine during the acute phase and were partial responders (CGI-I = minimally improved) will enter the continuation phase on 40mg fluoxetine, and will have their dose increased to 60mg. Partial responders will meet with the psychiatrist biweekly for the first 2 months and monthly for the second 2 months. Adolescents who received only IPT-A during acute phase and were partial responders (CGI-I = minimally improved) will begin treatment with fluoxetine during the continuation phase, in addition to continuing their IPT-A treatment. The dosage schedule will be 10mg per day for the first week and 20mg per day for the following 5 weeks. If no treatment response is observed by the 6th week, the dosage can be increased to 40mg per day. Pharmacotherapy sessions will be scheduled weekly for the first 4 weeks and biweekly thereafter.

Assessments. Adolescents will enter continuation treatment at week 16. Assessments will be conducted at week 24 and 32. The week 32 evaluation is already funded through the K23 study.

7 Statistical Plan

7.1 Sample Size Determination

Statistical experts warn against over-interpreting pilot data for estimating power and effect sizes for larger clinical trials.[51] Consequently, the proposed research study does not aim to evaluate the efficacy of the adaptive treatment strategies. Rather, the sample size was determined by the study aims which are to demonstrate the feasibility and acceptability of implementing the adaptive treatment strategies. With these aims in mind, an intent-to-treat sample size of 30 was selected. A sample size of 30 will help ensure there are enough depressed adolescents in each adaptive treatment strategy to assess feasibility and acceptability.

7.2 Statistical Methods

All statistical analyses will be conducted on the intent-to-treat sample.

- Hypothesis 1: Among families in the acute phase study who are eligible to participate in continuation treatment, the percentage of adolescents and parents

who consent to participate in the continuation treatment, and associated 95% confidence intervals will be calculated.

- Hypothesis 2: The mean/median (depending on the distribution) number and proportion of sessions attended by adolescents, as well as the associated 95% confidence intervals, will be calculated. The proportion of adolescents dropping out of treatment prematurely, and the associated 95% confidence interval, will be calculated.
- Hypothesis 3: An overall mean treatment satisfaction rating, and associated 95% confidence interval, will be calculated based on adolescents' and parents' responses on the CSQ-8.
- Hypothesis 4: An overall mean treatment satisfaction rating and the associated 95% confidence interval will be calculated based on clinicians' response on the clinician satisfaction measure.
- Hypotheses 5 & 6: (1) Primary analyses will examine within-subject change scores in CDRS, C- SSRS and CGAS over the course of acute and continuation treatment using repeated measures analysis of variance (ANOVA). Linear regression and analysis of covariance (ANCOVA) adjusting for pre-treatment scores will also be used to analyze changes in adolescents' outcomes. The magnitudes of changes in outcomes variables over time will be assessed using the paired t-test or Wilcoxon signed-rank test for continuous variables. Mixed-effects regression models will also be employed to compare CDRS, C-SSRS, and CGAS scores over multiple time points in order to obtain information on specific patterns of change over time. (2) Secondary analyses comparing within-subjects change scores across treatment groups on self-report measures of depression (BDI-II) and functioning (CBQ, SAS-SR) will be conducted using two-sample t-test, Wilcoxon rank sum test, and linear regression analysis. Hierarchical linear modeling (HLM) will also be conducted to compare scores over multiple time points within each treatment group. (3) Recovery will be defined as an absence of depression symptoms on the KSADS-PL for at least 8 weeks. Relapse will be defined as the reemergence of 5 or more symptoms of depression on the KSADS-PL. The percentage of adolescents who meet recovery criteria, and associated 95% confidence interval will be calculated. The percentage of adolescents who meet relapse criteria, and associated 95% confidence interval will be calculated. For those with a relapse, the mean (SD) time from recovery to relapse will be calculated.

Exploratory Analyses: Exploratory analyses will be conducted to determine whether comorbid psychiatric disorders, baseline severity of depression, and different forms of functioning (CBQ, SAS-SR, CGAS) predict or moderate positive or negative treatment outcomes. Potential predictors and moderators will be used to refine the personalized treatment strategy that will be tested in the subsequent R01.

7.3 Subject Population(s) for Analysis

All populations.

8 Safety and Adverse Events

8.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event (SAE***) is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization lasting >24 hours or prolonged hospitalization should be documented and reported as a **serious adverse event** unless specifically instructed otherwise in this protocol. Any condition responsible for surgery will be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all

adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events

8.3.1 Study Sponsor Notification by Investigator

A serious adverse event must be reported by telephone within 24 hours of finding out of the event. A Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to:

University of Minnesota, Office of the Vice President of Research
facgrant@umn.edu
(612) 625-2356

Minnesota Medical Foundation
giving@umn.edu
(612) 624-3333

At the time of the initial report, the following information should be provided:

- Study identifier
- Study Center
- Subject number
- Name of the drug/device
- A description of the event
- Date of onset
- Current status (on-going, resolved)
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator must provide further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information of ongoing serious adverse events should be provided promptly to the study sponsor.

8.3.2 IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) must be submitted to the IRB within 10 working days if it falls under the UPIRTSO guidelines.

8.3.3 FDA Notification by Sponsor

The study sponsor shall notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days from the sponsor's original receipt of the information.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

8.4 Stopping Rules

Adolescents will enter continuation treatment at week 16. Assessments will be conducted at week 24 and 32. The adolescent completes the BDI-II at each therapy session, and therapists assess suicidality and change in adolescents' clinical status using the CGI-I and CGI-S at each therapy session. The subject will be evaluated by *an independent safety monitor* if at any time any of the following occur: 1) a suicide attempt, 2) serious suicidal ideation (with a plan and/or intent) and refusal to contract for safety, 3) psychiatric hospitalization, 4) possible need for psychiatric hospitalization, or 5) significant worsening of depressive or other clinical symptoms (CDRS-R> 76 or CGI improvement score> 5). Adolescents will be removed from the study immediately following review if the *independent safety monitor* deems that the patient requires treatment outside of study protocols or if the treatment provided in the study is contraindicated. In these cases, the family will be provided with referrals to receive treatment out of the protocol.

While fluoxetine is generally well tolerated, side effects can occur. Adverse events will be closely monitored during each psychopharmacological treatment visit using the C-SSRS and the Side Effects forms. The study psychiatrist will review with families the following potential fluoxetine related adverse events: gastrointestinal complaints (nausea, pain, diarrhea, and constipation), dizziness, allergic reactions, increased anxiety or irritability, increased activation/restlessness, sleep changes (increased or decreased), sexual side effects, appetite changes (increase or decrease), unusual thoughts, sweating, fatigue, suicidal ideation/attempts/and or behaviors. In addition to these issues, the study psychiatrist will make the adolescents and their families aware of the Food and Drug Administration advisory that the use of antidepressants like the SSRIs may lead to suicidal thinking/attempts in depressed youths and that the FDA has placed product warning label with information highlighting the need for close observation for worsening of depression and the emergence of suicidality in children treated with these medications. This information will be a part of the consent process for the study so that families are aware of these issues when considering participation in

the study. The study psychiatrist will review with the adolescents and their legal guardians, potential adverse events and the need to carefully monitor for any significant changes in mood, thinking, behaviors, and physical symptoms especially early in treatment. The adolescents and their families will be instructed to call the study psychiatrist with any concerns, and to page the PI with any urgent clinical issues that emerge in between treatment sessions. The PI will call the study psychiatrist, who will follow up with the family. In the event of minor side effects (e.g., mild headaches), the medication may be maintained at the current dose levels or reduced. If any adverse medication reactions do occur, the medication will be withdrawn and clinical staff will follow the patient closely until the adverse reaction remits.

8.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.5.1 Internal Data and Safety Monitoring Board

The PI will maximize the safety and privacy of all study participants and ensure the integrity, validity, and confidentiality of data collection procedures through regular monitoring of clinical and research activities during weekly project meetings with the study staff. At the start of each treatment session, clinicians will be required to ask both adolescents and parents whether any adverse events or suicidality have occurred in the past week. Clinicians will report to the PI any serious or unexpected adverse events, unexpected problems that involve risk to the participants or others, and any breaches of confidentiality. The PI will report these to the Quorum within 24 hours of their occurrence. The PI will also submit an annual progress report to the IRB summarizing the data and safety monitoring activities and outlining 1) whether participants' safety, privacy and confidentiality has been consistently assured, 2) whether research instruments have been administered in a uniform manner and in a way that protects participants' privacy, 3) progress towards recruitment goals, quality of data collection (e.g., appropriate completion of forms), and participant retention/ attrition rates, and 4) a review of new scientific literature pertinent to the safety of participants or the ethics of research participation. The study psychiatrists, *the independent safety monitor,* psychologists, research clinicians, and clinical interviewers will take all appropriate actions to prevent and treat psychiatric emergencies in participating adolescents and family members as outlined in the Procedures to Minimize Potential Risks.

On an annual basis, the PI and Dr. Mufson will monitor the safety, quality and conduct of this study and decide whether adequate subject safeguards are in place. They will review: 1) the progress of the proposed study, including assessments of data quality and participant recruitment, accrual and retention; 2) outcome and adverse event data to determine whether there is any change to the anticipated benefit-to-risk ratio of study

participation and whether the study should continue, be changed, or terminated; 3) external factors or relevant information (e.g., pertinent scientific literature reports or therapeutic developments, results of related studies) that may have an impact on the safety of study participants or the ethics of the research study; and 4) study procedures designed to protect the privacy of the research subjects and the confidentiality of their research data.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

All research forms and audiotapes of the treatment sessions will contain the study assigned subject ID number only as identifying information. Research forms and will be kept in a locked file cabinet at the University of Minnesota. Clinical records will be kept in a separate locked file cabinet at the University of Minnesota. Only research staff and the treating clinical staff will have access to the research and clinical files.

Confidentiality will be strictly maintained. In order to safeguard the confidentiality and security of data files, computer accounts containing data will be password protected. Identifying information, records, and audio/ videotapes of clinical interactions will be stored in a locked cabinet in a locked office, only accessible to research staff members; a participant identification number will identify all materials. Participant identification numbers will be unrelated to participant characteristics (e.g. date of birth, social security number), and a list with the pairings of names and identification numbers will be kept in a separate password protected document a network drive, separate from the data files and tapes. All staff will sign confidentiality statements.

All tapes will be coded by subject identification number and date All audio files, none of which contain PHI, will be saved on an electronic shared folder to which only research staff have access. Audio files are saved for 3 years. During the consent process, participants have the ability to request deletion of audio files after three years, or allow staff to save the files indefinitely for research purposes. Files will be deleted after 3 years if the participant chooses the former option. If the adolescent and the parent response differ regarding the retention of audio files for training of future research staff, the answer is to retain the audio files is no.

All subjects will be informed during the consent process that their information will be kept strictly confidential unless information is revealed suggesting that the subject or someone else is in danger (e.g., prostitution, IV drug use, child abuse (see below), suicidality, homicidality). Prior to eliciting this information, the child will be fully informed that the clinician may need to report such information. Before parents will be made aware of this information, our procedure will be to first talk with the child and explain what information will be disclosed to parents. Because information relating to abuse will be assessed, participants will be informed of the need to report child abuse prior to eliciting this information. All staff will follow federal and state child abuse reporting requirements.

Participants will be assigned a coded identification number that will be used on all data collection measures. To minimize the risk of loss of confidentiality, the data collected in this study will be protected by the use of separate data files. The first will include the subject consent forms, names, addresses, telephone numbers, date of birth, and subject ID. Other databases will include the questionnaire data from the project, and participants' study ID will be the only unique piece of information linking the data files to the consent file. Audio files of assessment and treatment sessions will be stored in a separate storage area online. Only study IDs will be used to link audio files to questionnaire data. These files will all be password protected and accessible to only a limited number of project personnel. The collected materials will be used only for research purposes; participants' records with identifying information will not be released to anyone without participants' written permission. The databases will be password protected and the database password will be changed on a regular basis. The Department's computing system is protected from outside access. All staff members will be required to close password-protected applications or lock their workstations when they are away from their desks. All paper forms will be kept in locked file cabinets at the University of Minnesota. During data analysis all identifying information, with the exception of the participant identification number is removed from the data. No information about identities of the study participants will be published or presented at conferences.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts,

laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. Data may be transcribed legibly on case report forms supplied for each subject or directly inputted into an electronic system or any combination thereof.

9.3 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 6 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 6 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according to FDA/GCP guidelines. (Explain who will be monitoring what sites or self-monitoring according to the U of M plan. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

The PI will maximize the safety and privacy of all study participants and ensure the integrity, validity, and confidentiality of data collection procedures through regular monitoring of clinical and research activities during weekly project meetings with the study staff. At the start of each treatment session, clinicians will be required to ask both adolescents and parents whether any adverse events or suicidality have occurred in the past week. Clinicians will report to the PI any serious or unexpected adverse events, unexpected problems that involve risk to the participants or others, and any breaches of confidentiality. The PI will report these to the Internal Review Board (IRB) at the University of Minnesota within 24 hours of their occurrence. The PI will also submit an annual progress report to the IRB summarizing the data and safety monitoring activities and outlining 1) whether participants' safety, privacy and confidentiality has been consistently assured, 2) whether research instruments have been administered in a

uniform manner and in a way that protects participants' privacy, 3) progress towards recruitment goals, quality of data collection (e.g., appropriate completion of forms), and participant retention/ attrition rates, and 4) a review of new scientific literature pertinent to the safety of participants or the ethics of research participation. The study psychiatrists, *the independent safety monitor* psychologists, research clinicians, and clinical interviewers will take all appropriate actions to prevent and treat psychiatric emergencies in participating adolescents and family members as outlined in the Procedures to Minimize Potential Risks.

On an annual basis, the PI and Dr. Mufson will monitor the safety, quality and conduct of this study and decide whether adequate subject safeguards are in place. They will review: 1) the progress of the proposed study, including assessments of data quality and participant recruitment, accrual and retention; 2) outcome and adverse event data to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation and whether the study should continue, be changed, or terminated; 3) external factors or relevant information (e.g., pertinent scientific literature reports or therapeutic developments, results of related studies) that may have an impact on the safety of study participants or the ethics of the research study; and 4) study procedures designed to protect the privacy of the research subjects and the confidentiality of their research data.

10.2 Auditing and Inspecting

The investigator will permit study-related audits and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

This study is financed through grants from the University of Minnesota Foundation and University of Minnesota Office of Vice President of Research

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must refer to the Regents Policies on Individual Conflict of Interest Policy or Institutional Conflict of Interest Policy. These policies require University Faculty and staff to report external professional activities and business and significant financial interests related to his or her University activities by submitting a REPA (Report of External Professional Activities) at least once per year. Faculty and staff should also file a REPA when substantial changes in business or financial interests occur, when an activity that presents a potential conflict of interest is anticipated, or when submitting an application for research support or technology transfer, submitting research protocols to the IRB, or receiving financial contributions. All University of Minnesota investigators will follow the University conflict of interest policy.

12.3 Subject Stipends or Payments

The adolescent will receive $30 in cash directly after the week 24 evaluation and the parent will receive $10 in cash for the week 24 evaluation.

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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