## PROTOCOL TITLE:
An Adaptive Algorithm-Based Approach to Treatment for Adolescent Depression

## PROTOCOL NUMBER: 25767

## PRINCIPAL INVESTIGATOR or FACULTY ADVISOR:
Meredith Gunlicks-Stoessel, Ph.D., L.P.
Department of Psychiatry, Division of Child and Adolescent Psychiatry
612-273-9844
mgunlick@umn.edu

## STUDENT INVESTIGATOR:
None

## VERSION NUMBER/DATE:
Version 27 (09/05/2023)

## Table of Contents

## ABBREVIATIONS/DEFINITIONS

- AE Adverse Event
- ATA Adaptive Treatment Attitudes Questionnaire
- ATA-T Adaptive Treatment Attitudes – Therapist Questionnaire
- ATS Adaptive Treatment Strategy
- BDI-II Beck Depression Inventory-II
- CASA Child and Adolescent Services Assessment
- CBQ Conflict Behavior Questionnaire
- CDRS-R Children's Depression Rating Scale-Revised
- CGAS Children's Global Assessment Scale
- CSQ-8 Client Satisfaction Questionnaire
- C-SSRS Columbia Suicide Severity Rating Scale
- CGI Clinical Global Improvement
- DSMB Data and Safety Monitoring Board
- EBPAS-36 Evidence-Based Practice Attitude Scale-36
- ET Expectations for Treatment
- HRSD Hamilton Rating Scale for Depression
- IC Issues Checklist
- IE Independent Evaluator
- IPPA Inventory of Parent and Peer Attachment
- IPT-A Interpersonal Psychotherapy for Depressed Adolescents
- ISM Independent Safety Monitor
- K-SADS-PL Schedule for Affective Disorders and Schizophrenia for School-aged Children – Present and Lifetime Version
- ORCA Organizational Readiness to Change Assessment
- SAE Serious Adverse Event
- SASC Sociotropy-Achievement Scale for Children
- SMART Sequential Multiple Assignment Randomized Trial
- SOCQ Stages of Change Questionnaire
- SSRI Selective Serotonin Reuptake Inhibitor
- TP Treatment Preference
- UC Usual Care

# STUDY SUMMARY

| | |
|---|---|
| **Study Title** | An Adaptive Algorithm-Based Approach to Treatment for Adolescent Depression |
| **Study Design** | Phase II Clinical Trial<br>(Sequential Multiple Assignment Randomized Trial; SMART) |
| **Primary Objective** | Evaluate the effectiveness of the two adaptive treatment strategies (ATSs) as compared to usual care (UC) |
| **Secondary Objective(s)** | • Evaluate adolescents' interpersonal functioning as a treatment target of Interpersonal Psychotherapy for Depressed Adolescents (IPT-A)<br>• Evaluate moderators of initial treatment and treatment augmentation strategies.<br>• Conduct an implementation-focused process evaluation to identify barriers and facilitators that influenced ATS implementation.<br>• Examine genetic variants, gene expression, and DNA methylation signatures in relationship to treatment response and symptoms |
| **Research Intervention(s)/Investigational Agents** | • Interpersonal Psychotherapy for Depressed Adolescents (IPT-A)<br>• Selective Serotonin Reuptake Inhibitors (SSRIs)<br>• Usual Care (UC) |
| **IND/IDE # (if applicable)** | N/A |
| **Investigational Drug Services # (if applicable)** | N/A |
| **Study Population** | • Adolescents (age 12-18) with a diagnosis of a depressive disorder and their parents<br>• Clinic staff |
| **Sample Size (number of participants)** | • 200 adolescents and their parents<br>• 50 clinic staff members |
| **Study Duration for Individual Participants** | 36 weeks |

# 1.0 Objectives

Adolescent depression is a prevalent and debilitating disorder that places youth at risk for suicidality, other psychiatric diagnoses, and functional impairment both during adolescence and into adulthood. There are a number of effective treatments; however, 30-50% of adolescents who receive these treatments do not respond. To improve response rates, practice parameters recommend routine systematic symptom assessment over the course of treatment to inform decisions regarding whether to switch or augment treatment. Unfortunately, routine symptom assessment in usual care for adolescent depression is extremely rare. In addition, for psychotherapy, which is the most frequent treatment for adolescent depression, there are currently no guidelines to direct therapists regarding how to use those symptom assessments to guide subsequent treatment decisions. Addressing this critical knowledge gap requires identifying (1) what symptoms or patient characteristics to assess, (2) when to administer those assessments, and (3) what subsequent treatment to provide, based on those assessments. Adaptive treatment strategies (ATSs) provide algorithms for guiding treatment decision making. These algorithms are based on patient characteristics and outcomes collected during the course of therapy, and they provide guidelines regarding when, how, and for whom midcourse changes in the treatment approach should be initiated. The purpose of the current study is to evaluate the effectiveness of two ATSs for adolescent depression. The ATSs include delivery of an evidence-based psychotherapy for adolescent depression (interpersonal psychotherapy, IPT-A), systematic symptom monitoring, and an empirically-derived algorithm that specifies whether, when, and how to augment IPT-A. Two hundred depressed adolescents (age 12-18) will be recruited to participate in a 16-week sequential multiple assignment randomized trial (SMART) conducted in outpatient community mental health clinics (PrairieCare Medical Group and Minnesota Mental Health Clinics). Adolescents will be randomized to the IPT-A ATS condition (N=134) or the community clinic's usual care (UC) (N=66). The aims of this study are to:

- Evaluate the effectiveness of the ATSs as compared to UC.
- Evaluate adolescents' interpersonal functioning as a treatment target of IPT-A
- Evaluate moderators of initial treatment and treatment augmentation strategies.
- Conduct an implementation-focused process evaluation to identify barriers and facilitators that influenced ATS implementation.
- Examine genetic variants, gene expression, and DNA methylation signatures in relationship to treatment response and symptoms

# 2.0 Background

The Public Health Problem of Adolescent Depression:
Depression is one of the most common psychiatric disorders in adolescents,[1] with approximately 20% of adolescents experiencing a depressive episode at some point during their teenage years.[2] It is associated with significant morbidity, mortality, and functional impairment[3,4] and is the largest predictor of completed suicides among girls and the second largest predictor among boys.[5] Adolescent depression imparts significant costs on families and society, including expenditures on health care services and lost work time for parents.[6,7] In addition, the psychiatric and psychosocial sequelae have been found to persist into adulthood.[8,9] Accordingly, the development of effective strategies for treating adolescent depression has significant implications for health and well-being both during adolescence and into adulthood.

Improving Outcomes and Clinical Practice by Developing Adaptive Treatment Strategies:
There are now a number of evidence-based treatments for adolescent depression including psychotherapy, antidepressant medication, and their combination.[10] Two psychotherapies have "well-established" empirical support: interpersonal psychotherapy (IPT-A) and cognitive behavioral therapy (CBT).[11] A number of antidepressant medications also have demonstrated efficacy,[12-16] and fluoxetine and escitalopram (both selective serotonin reuptake inhibitors, SSRIs) have approval by the Food and Drug Administration for use with adolescents. Despite progress in treatment development, approximately 30-50% of adolescents who receive these treatments do not respond.[17,18] To address this problem, practice parameters recommend systematic and routine assessment and monitoring of depression symptoms over the course of treatment to inform treatment planning, including decisions regarding whether to switch or augment treatment.[10,19] Several studies have shown that routine assessment improves treatment outcomes compared to no assessment conditions.[20-26] Importantly, progress monitoring can be easily implemented in community practice by integrating it into patients' electronic medical records (EMRs). EMRs can be programmed to alert clinicians to administer an assessment at a specified time point, the assessment data can be entered directly into the EMR, and the EMR can be programmed with the algorithms that guide subsequent treatment recommendations. This creates a user-friendly data-based decision support system that provides feedback on treatment progress and guides treatment planning.[27] Despite ample research support and available methods for implementation, *routine symptom assessment in usual care for adolescent depression is extremely rare*.[28] A recent review of EMRs from 3 large health care systems found that only 32% of depressed adolescents had documentation of symptom monitoring following the initial intake.[28] In addition, for psychotherapy, which is the most frequent treatment for adolescent depression,[28] there are *currently no guidelines* to direct therapists regarding how to use those symptom assessments to guide subsequent treatment decisions. As a consequence, if clinicians do decide to switch or augment treatment, they may do

so in a trial and error fashion, which could result in extended time to remission, unnecessary experience of side effects, or increased cost or other burdens.

Developing a guideline to inform treatment planning requires evaluating (1) what symptoms or patient characteristics to assess, (2) when to administer those assessments, and (3) what subsequent treatment to provide, based on those assessments. *Adaptive treatment strategies* (ATSs) provide algorithms for guiding treatment decision making. These algorithms are based on patient characteristics and outcomes collected during the treatment process, and they provide guidelines regarding when, how, and for whom midcourse changes in the treatment approach should be initiated. They can, for example, operationalize when to determine that a patient is not likely to respond if a treatment strategy is continued, what the next treatment should be, and at what dose or intensity. The development of evidence-based ATSs for adolescent depression not only has the potential to significantly improve treatment outcomes, but can also increase the efficiency and cost effectiveness of treatment by delivering treatments when and for whom they will do the most good.

ATSs are developed and evaluated within the context of sequential multiple assignment randomized trials (SMARTs).[29-31] In a SMART, subjects can be randomized multiple times, and these randomizations occur sequentially through time at selected critical decision points. The data collected in a SMART are used to infer the expected results under different treatment strategies and to determine the ATS leading to the most favorable outcomes. We propose to develop an algorithm-based ATS for adolescent depression that follows a stepped-care model of health care delivery. Stepped-care models recommend selecting an initial treatment that is the least restrictive among available empirically-based treatments.[32] “Least restrictive” refers to all restrictions on the patient’s life and resources, including cost, physical effects of the treatment, and interference in the patient’s lifestyle. Treatments that are more restrictive (but potentially more effective) are reserved for patients who do not respond to the initial treatment. In this way, a stepped-care approach aims to achieve a positive treatment outcome with as little treatment as possible, which maximizes clinical benefits, minimizes burdens, and leads to more efficient and cost effective service delivery. Stepped-care models have demonstrated feasibility and effectiveness in improving a variety of outcomes,[33-35] including youth depression.[36]

Stage 1 Treatment:
We propose two ATSs that begin with psychotherapy. Psychotherapy does not carry a risk of adverse physical side effects, it is the most frequent treatment for adolescent depression,[28] and many families report a preference for psychotherapy over medication.[37-39] The psychotherapy provided will be interpersonal psychotherapy for depressed adolescents (IPT-A).[40] IPT-A aims to address a key mechanism in the development and resolution of adolescent depression:

disruptions in interpersonal relationships (attachment/affiliation subconstruct of the Systems for Social Processes in the NIMH Research Domain Criteria (RDoC) matrix).[41-43] IPT-A teaches skills that can address the relationship difficulties most closely related to the onset or maintenance of the adolescent's depression. IPT-A has strong empirical support and has been implemented successfully in real-world settings.[17,44,45] While CBT has been the focus of a greater number of empirical studies than IPT-A, the uptake of CBT in community practice has been underwhelming,[46] and many challenges have been described in training community clinicians in CBT.[47] The most frequently used therapy approaches for adolescent depression in community practice are family-based and psychodynamic.[48] Given that the therapy approaches in IPT-A may be a bit more consistent with usual care, IPT-A may be an easier treatment approach to disseminate. The IPT-A treatment manual has been published by Guilford Press, and online training in IPT-A is also recently available via the Society of Clinical Child & Adolescent Psychology website (www.effectivechildtherapy.com), thus significantly increasing the feasibility of uptake of this intervention in community settings.

The Adaptive Treatment Algorithm:
Using data from a previous clinical trial of IPT-A, we examined whether there were early indicators of IPT-A treatment response that could be used to guide decisions regarding whether and when to intensify or augment treatment. We found that depressed adolescents who begin treatment with IPT-A can be classified as likely or not likely to respond to a full course of IPT-A (12 sessions delivered over 16 weeks) at week 4 and at week 8 of treatment (Preliminary Study 1).[49] At week 4, a cutoff of a 20% reduction in symptoms on the Hamilton Rating Scale for Depression (HRSD)[50] represented the best combined sensitivity and specificity for predicting response status post-treatment (week 16). At week 8, a 40% reduction in symptoms was required to predict week 16 response. The HRSD has demonstrated feasibility and reliability in community settings.[50] It provides standardized feedback to clinicians and decreases idiosyncrasies that occur when clinicians make treatment decisions without use of a standardized measure.

Stage 2 Treatments:
For insufficient responders to IPT-A, we propose to test two approaches to intensifying treatment during stage 2: the addition of an SSRI and more intensive IPT-A (delivered twice per week). Five studies have examined the efficacy of a combination of psychotherapy and medication in comparison to psychotherapy alone and/or medication alone.[18,51-54] Three studies found that the combined treatment approach was significantly more efficacious than monotherapy,[18,51,52] whereas the other two did not.[53,54] Thus, adding an SSRI to IPT-A may be an effective option for some adolescents, though research support is not unequivocal. Studies have also found that psychotherapy delivered on a twice a week basis is

an effective treatment approach for depression.[55-58] Most insurance panels will permit billing for twice per week sessions. Given many families' preference for psychotherapy over medication,[37-39] intensifying the therapy rather than adding an SSRI may yield more promising results because it is a more patient-centered treatment approach for some families. Attending therapy twice per week does add additional burden to families; however, it is time limited (4 weeks), and in our pilot study (Preliminary Study 2), we developed some strategies for increasing motivation and problem-solving obstacles, which resulted in good session attendance. To summarize, there are two ATSs embedded in our trial design:

ATS 1: Psychotherapists initiate weekly IPT-A.[17,40,59] If at week 4 the adolescent has shown at least a 20% reduction in depressive symptoms, continue IPT-A. If at week 8, the adolescent has shown at least a 40% reduction in symptoms, continue IPT-A (12 sessions total). If the adolescent has not shown a sufficient reduction at week 4 or week 8, refer the adolescents to a psychopharmacologist to *add an SSRI and continue weekly IPT-A sessions* (12 sessions total).

ATS 2: Psychotherapists initiate weekly IPT-A.[17,40,59] If at week 4 the adolescent has shown at least a 20% reduction in depressive symptoms, continue IPT-A. If at week 8, the adolescent has shown at least a 40% reduction in symptoms, continue IPT-A (12 sessions total). If the adolescent has not shown a sufficient reduction at week 4 or week 8, *increase dose of IPT-A* by scheduling sessions twice a week for *4* weeks; then return to weekly IPT-A (*16* sessions total).

Further Refinement of the ATSs, Including Evaluation of Treatment Target Engagement:
In this study, we are hypothesizing that our adaptive treatment algorithm, based on change in depression at weeks 4 and 8, will produce significantly better outcomes than usual care, in which therapists make decisions about treatment planning using their usual methods. However, we also expect that incorporating assessment of other patient characteristics, in addition to depressive symptoms, into the decision of whether and how to change treatment will likely increase the response rates further. NIMH's new focus on experimental therapeutics is highly relevant here.[60,61] In the experimental therapeutics paradigm, intervention evaluation focuses first on whether the intervention has an impact on the intervention's proposed mechanism of action or "treatment target," and second, on whether "target engagement" produces the proposed clinical effect.[60,61] SMARTs are ideal clinical trial designs for this. They have the distinct advantage of providing the opportunity to examine the impact of treatment target engagement during the initial (stage 1) treatment on the effectiveness of the subsequent (stage 2) treatment approach in a treatment sequence. For IPT-A, whose purported mechanism of action is improvements in interpersonal relationships, we can examine degree of improvement in adolescents' interpersonal relationships during stage 1 (i.e. degree of target engagement), as a

tailoring variable for selecting the subsequent stage 2 treatment. At stage 2 in the current study, insufficient responders are randomized to an increased dose of IPT-A or the addition of an SSRI. In this way, we can evaluate, among the insufficient responders who did not demonstrate target engagement, the comparative effectiveness of intensifying psychotherapeutic work on interpersonal skills to attempt to better engage the treatment target versus adding a different treatment approach (SSRI) that will address a different treatment target. The advantage of the SMART design is that stage 2 treatment assignment is not confounded with the tailoring variable (due to randomization), making inference on the effect of tailoring treatment less prone to bias.

In addition to measures of IPT-A target engagement, we will also explore additional moderators of stage 2 treatments for insufficient responders to further refine the ATSs. The moderators selected represent previously identified predictors of IPT-A specifically or treatment for depression generally, and include: patient treatment preference,[62,63] expectation of treatment outcome,[64] sociotropy (a personality trait representing the degree to which one's self-concept and well-being are dependent on the how things are going in one's relationships),[65] depression severity,[17] comorbid diagnoses,[66] and stage 1 treatment attendance.[67]

Genetic and Epigenetic Relationships with disease risk and treatment response: The causality of mood disorders is complex and involves the interplay between genetic predisposition and non-genetic biological, psychological, and social factors. Studies have shown that mood disorders such as major depressive disorder are highly heritable, with genetic factors contributing 31-42% of disease risk.[68] Since the completion of the Human Genome Project, research has identified multiple candidate genes displaying variable contributions to the risk of depression. Due to the wide variability in therapeutic response to SSRIs in the treatment of depression, studies have also focused on identifying pharmacogenetic predictors of drug response which would aid in therapeutic and dosing selection currently performed in 'trial and error' approaches. Earlier studies utilizing a hypothesis-driven, candidate gene study design to assess the relationship between genetics and SSRI treatment response in patients with depression focused on genes of the serotonergic, dopaminergic, glutamatergic, monoaminergic, neurotrophic and hypothalamic-pituitary-adrenal (HPA) axis systems: *COMT,*[69,70] *HTR2A,*[71-73] *HTR1A,*[74] _ENREF_74 *CNR1,*[74] _ENREF_75 *SLC6A4,*[75] *NPY,*[76] *MAOA,*[70,77] *IL1B,* [70,78] *GRIK4,*[79] *BDNF,* [70,72] *GNB3*,[70] *FKBP5*,[72] and *ABCB1.*[70,80] In addition, studies investigating the wide variability in SSRI treatment response have also investigated multiple pharmacokinetic markers, namely three cytochrome P450 (CYP) hepatic enzymes CYP2C19, CYP2D6, and CYP3A4, involved in SSRI metabolism. Previous studies have shown that genetic differences in *CYP2C19* and *CYP2D6* have been associated with differing serum concentrations of SSRIs such as escitalopram as well as treatment response.[73,81-83]

Multiple studies have also utilized hypothesis-generating, genome-wide association study (GWAS) approaches,[84-87] although this work has primarily focused on adult populations with a need for investigations in younger patients. Nevertheless, analysis of antidepressant response data using a mixed linear model approach to estimate the proportion of phenotypic variance explained by genome-wide polymorphisms has shown that common genetic variants explain a considerable proportion of individual differences in antidepressant response which has thus prompted further pharmacogenomic studies.[88]

Despite the relatively high heritability of depression, there is considerable discordance within monozygotic twin pairs, implicating a role for non-genetic, presumably environmental, factors.[89] One mechanism by which external environmental stimuli can have an impact on individual development is via epigenetic changes to gene expression. Epigenetics refers to dynamic modifications of the DNA structure influencing gene regulation that do not involve altering the DNA sequence. Exposure to pharmaceuticals, nutrition, exercise, and stress are capable of producing positive and negative epigenetic modifications with lasting effects on human development, metabolism and health.[90] To date, DNA methylation is the most studied epigenetic modification. Previous studies suggest that DNA methylation plays a role in stress-related psychiatric disorders and, more specifically, in the development and treatment of depression.[91] Early epigenetic studies in rodents focused on the promoter region of the glucocorticoid receptor gene *NR3C1* and showed that maternal behavior and environment alters methylation profiles in hippocampal tissue, and that environmental improvement removed the differences in epigenetic profiles and improved the impaired stress response.[92] In terms of treatment of depression, studies have also indicated that multiple antidepressants and mood stabilizers may exert part of their therapeutic action through epigenetic modification of DNA methyltransferase I (DNMT1) or histone deacetylase inhibition, altering methylation levels and thus affecting gene expression.[93] To date, the majority of epigenetic studies investigating relationships with antidepressant treatment response have used a targeted approach examining a limited number of DNA methylation sites within specific gene loci, including *SLC6A4*, *BDNF*, *FKBP5*, *OXTR*, *IL11*, and *MAOA*.[89]

Though much research has been performed in assessing the relationships between genetic and epigenetic markers with risk of depression, symptom severity, and treatment response, the majority have focused on adult patients and SSRI treatment modalities. The current trial provides a unique opportunity to retrospectively investigate genetic and epigenetic signatures in a well-defined cohort of adolescents diagnosed with depression. Furthermore, this trial focuses on non-pharmacological treatment interventions, namely interpersonal psychotherapy for adolescents. Genetic and epigenetic research utilizing this cohort of patients may aid in identifying genetic markers (gene polymorphisms or expression) or epigenetic signatures (DNA methylation levels) that correlate with difference in response to non-pharmacological treatment interventions, or identify

individuals who would benefit from the addition of SSRI treatment. Utilizing saliva collected longitudinally over the treatment course also offers significant benefits due to the non-invasive nature and ease of collection as well as the ability to detect DNA methylation and gene expression changes over treatment time.

Implementation:

The primary aim of this study is to validate the algorithm that is the basis of the adaptive treatment strategies proposed in this project. We have designed the ATSs to maximize the potential for implementation in community practice by 1) using an intervention that is easily accessible to professionals, 2) basing our treatment algorithms on an assessment measure that is free and available for public use, and 3) automating the treatment algorithm in a user-friendly web-based program. In addition, we propose to integrate some components of implementation research into our effectiveness study to inform and facilitate future dissemination and implementation of these ATSs into broad clinical practice. Following Curran et al,[94] we will follow a hybrid type I effectiveness-implementation design that tests the effects of the ATSs on clinical outcomes, while also observing and gathering information on implementation. Hybrid type I studies focus on process evaluations of barriers and facilitators to uptake/adoption efforts, and on identifying tools and training that would facilitate future implementation. Information is collected not only from patients and providers, but also from clinical and organizational leaders who would be responsible for rolling out the clinical intervention. Our process evaluation is informed primarily by the RE-AIM framework (Reach, Effectiveness, Adoption, Implementation and Maintenance).[95,96] Reach refers to how many eligible patients agree to the intervention. Effectiveness evaluates the intervention's clinical outcomes. Adoption refers to the decision of the leadership and staff at the targeted settings to implement the intervention. Implementation refers to whether the intervention is implemented with high fidelity and consistency, as well as the cost of the intervention. Maintenance (not assessed in this study) refers to whether the clinical intervention is sustained after implementation support is withdrawn. We also include two elements from the Promoting Action on Research Implementation in Health Services (PARIHS) framework: (1) Evidence: the extent to which providers and staff believe there is research evidence, as well as a clinical need for the new intervention, and (2) Context: provider and staff perception of the organization's leadership culture, staff culture, leadership feedback, readiness to change, and resources to support to new intervention. The results of the process evaluation will be used to inform future implementation efforts.[97,98]

Preliminary Data:

1. Early Prediction of Treatment Response with IPT-A (Gunlicks-Stoessel & Mufson, 2011).[49] These data support the selection of the time points and criteria for classifying adolescents who begin treatment with IPT-A as "likely to respond"

or "not likely to respond" by the end of a 16-week course of IPT-A. 34 adolescents participating in an RCT of IPT-A versus treatment as usual in school-based health clinics were randomized to receive 12 sessions of IPT-A delivered over 16 weeks.[17] The HRSD[99] was administered by blinded evaluators at weeks 4, 8, 12, and 16. Receiver operating characteristic (ROC) analysis identified week 4 and week 8 as the best time points for predicting post-treatment (week 16) response (week 4: AUC=.78, p=.01; week 8: AUC=.81, p=.00). At week 4, a cutoff of 20% reduction in HRSD from baseline represented the best combined sensitivity (72.7%) and specificity (71.4%) for predicting post-treatment response. At week 8, a cutoff of 40% reduction in HRSD from baseline represented the best combined sensitivity (72.7%) and specificity (83.3%).

2. A Pilot SMART of 4 ATSs Beginning with IPT-A (Gunlicks-Stoessel et al., 2016).[38] These data support the feasibility, acceptability, and preliminary efficacy of the two proposed ATSs. Forty adolescents with a depression diagnosis enrolled in a 16-week SMART, with an initial treatment plan of 12 sessions of IPT-A. Adolescents were randomized to a week 4 or a week 8 decision point for identifying potential non-responders. Adolescents who were classified as sufficient responders ($\geq$ 20% reduction in HRSD[99] at week 4 or $\geq$ 40% reduction in HRSD at week 8) continued the initial treatment plan of 12 IPT-A sessions. Adolescents who were classified as insufficient responders were randomized a second time to the addition of fluoxetine (FLX) or an additional 4 IPT-A sessions scheduled twice a week (increase from 12 to 16 sessions). The SMART study procedures and ATSs were feasible and acceptable to families and therapists.

a. Subject Recruitment, Adherence, and Retention. 145 adolescents were pre-screened by telephone, 63 signed consent/assent, and 40 were randomized. These rates are comparable or better than other published clinical trials of treatments for adolescent depression.[18,36,100,101] Adherence and retention were high (see below):

| Stage 2 Treatment | Number who Initiated Stage 2 Treatment | Randomized Treatment Plan | Mean (SD) Session Attendance | Completed Treatment |
|---|---|---|---|---|
| No Change (n = 17) | 17/17 | 12 IPT-A sessions | 11.2 (1.8) | 14/17 |
| Add Medication (n = 11) | 10/11 | 12 IPT-A sessions 6-8 medication sessions | 11.7 (1.4) IPT-A 5.3 (2.6) medication | 9/11 |
| Increase IPT-A (n = 11) | 10/11 | 16 IPT-A sessions | 15.4 (.9) | 8/11 |

* One adolescent dropped out prior to determination of stage 2 treatment

b. Therapist Fidelity. Twelve therapists, eleven of which had no prior experience delivering IPT-A, delivered the ATSs in this study. Therapists were adherent to

implementation of the ATSs. 100% of therapists administered HRSD at appropriate session and initiated and communicated the appropriate stage 2 treatment to families. Interrater reliability of the HRSD (Pearson's r) was .82. Therapists' HRSD ratings at week 4 and 8 were correlated with Independent Evaluators' CDRS-R ratings (week 4: r = 78, p = .00; week 8: r = .63, p=.00).Therapists also implemented IPT-A with a high level of adherence (mean adherence = 3.30 on scale of 1 to 4).

c. ATS Acceptability. Adolescents' and parents' treatment satisfaction (CSQ-8) was high (adolescents: M = 27.2, SD = 3.9; parents: M = 27.0, SD = 4.0).

d. Parents' and Adolescents' Attitudes Regarding Medication and More Intensive Therapy. These data support (1) parents' preferences for a stepped-care model of treatment that begins with therapy only, and (2) parents' preference for augmenting treatment for insufficient responders by increasing the dose of IPT-A. Prior to treatment, adolescents and parents reported their attitudes regarding the possible type of change to the treatment plan for insufficient responders. They also reported their attitudes right after they were informed of the change to treatment and at week 16. Prior to treatment, many parents reported negative attitudes regarding adding medication (37% neg, 33% neu, 30% pos) and were more positive about the possibility of increasing the dose of IPT-A (70% pos, 22% neu, 7% neg). Among parents of insufficient responders who were randomized to add medication, most parents reported feeling negative about adding medication right after they were informed of the change (60% neg, 20% neu, 20% pos). By post-treatment, 50% felt positive, 25% felt negative, and 25% felt neutral. All parents of adolescents randomized to increased IPT-A felt positively about the change both right after they were informed of the change and post-treatment. Most adolescents reported feeling positive about both treatment augmentation strategies at both pre-treatment (add meds: 46% pos, 31% neu, 23% neg; increase IPT-A: 54% pos, 23% neu, 23% neg) and post-treatment (add meds: 71% pos, 14% neu, 14% neg; increase IPT-A: 80% pos, 20% neu, 0% neg).

e. Treatment Outcomes. It was better to begin assessing for insufficient response and altering the treatment plan at week 4 rather than waiting until week 8 to make to first assessment and possible treatment change. Outcomes for insufficient responders randomized to add FLX or increase the dose of IPT-A are below:

| | Week 4 M (SD) | Week 8 M (SD) | ES (d) | Insufficient Responder: Add FLX M (SD) | Insufficient Responder: Increase IPT-A M (SD) | ES (d) |
|---|---|---|---|---|---|---|
| Children's Depression Rating Scale<br>Baseline<br>Week 16 | 55.90 (10.36)<br>34.76 (13.29) | 55.25 (10.99)<br>41.06 (8.19) | .57 | 58.00 (11.00)<br>38.10 (10.51) | 56.45 (9.06)<br>37.75 (9.02) | .04 |
| Children's Global Assessment Scale<br>Baseline<br>Week 16 | 50.35 (5.17)<br>66.41 (15.28) | 51.65 (6.92)<br>60.44 (6.37) | .51 | 50.73 (6.48)<br>62.50 (14.70) | 49.64 (5.28)<br>63.25 (8.71) | .06 |
| Clinical Global Improvement<br>Week 16 | 2.25 (.97) | 2.80 (.95) | .57 | 2.64 (1.03) | 2.45 (.69) | .22 |

3. Feasibility of the Service Setting (Bloomquist, et al., in press).[102] Twenty-eight depressed adolescents participated in a pilot study of CBT adapted for delivery within an intensive outpatient program. Treatment involved 24 hours of CBT skills training for youth and 12 hours of CBT information/support for parents delivered in groups over six weeks. Out of 24 days delivered over six weeks, adolescents attended at high rates (mean 18.7 days or 78%; median 20 days or 83%) with a majority of parents attending the information parent groups. Fidelity indicators of program delivery derived from intermittent live research technician observations showed acceptable to high levels of fidelity (teen skills: adherence 82%, quality of delivery 85%; parent skills: adherence 70%, quality 98%). Adolescents demonstrated significant reductions in depressive symptoms (pre-treatment BASC-2:[103] M = 62.90, SD = 18.60, post-treatment: M = 55.50, SD = 12.78).

## 3.0 Study Endpoints/Events/Outcomes

Primary Endpoint/Event/Outcome: Children's Depression Rating Scale-Revised (CDRS-R)[104]

Secondary Endpoint(s)/Event(s)/Outcome(s): Beck Depression Inventory-II (BDI-II),[105] Clinical Global Improvement (CGI),[106] Conflict Behavior Questionnaire (CBQ); Inventory of Parent and Peer Attachment (IPPA),[107] Issues Checklist (IC),[108] adolescents' and parents' perceptions of their interpersonal behaviors during a conflict negotiation task,[109,110] cost effectiveness, qualitative findings from the implementation-focused process evaluation, genetic variants, gene expression, DNA methylation levels.

# 4.0 Study Intervention(s)/Investigational Agent(s)

Description:

Interpersonal Psychotherapy for Depressed Adolescents (IPT-A).[40] IPT-A is an evidence-based intervention that aims to decrease depressive symptoms by helping adolescents improve their relationships and interpersonal interactions. It addresses one or more of four interpersonal problem areas: grief, role disputes, role transitions, and interpersonal deficits. The primary treatment techniques in IPT-A include emotion identification/expression, linking interpersonal events to mood, communication analysis, communication skill building, decision analysis, role playing, and assignment of interpersonal experiments (i.e. homework). In clinical trials, depressed adolescents treated with IPT-A demonstrated fewer depressive symptoms and better psychosocial functioning post-treatment than adolescents in control conditions.[17,59,111]

Selective Serotonin Reuptake Inhibitors (SSRIs). Fluoxetine, escitalopram, citalopram, fluvoxamine, and sertraline have demonstrated efficacy, with response rates of 40-60%.[12-16] Fluoxetine will be the first choice SSRI, given the literature supporting its efficacy and tolerability, and its FDA approval. Escitalopram will be the second choice since it has acquired FDA approval for adolescents. The psychopharmacologist may choose to select escitalopram first if clinically indicated when there is a previous history of intolerance to fluoxetine, based on family history or preference, and inability to achieve an adequate fluoxetine dose. Citalopram, fluvoxamine, and sertraline may also be selected first if clinically indicated, as above.

Usual Care (UC). UC psychotherapists will implement therapy procedures that they usually use and believe to be effective in clinical practice. The clinic directors characterize the psychotherapy currently provided in the clinics as "eclectic," with a combination of psychodynamic, client-centered, family-focused, and cognitive behavioral approaches utilized. Therapy will continue until the therapist and/or family decides to terminate services. Therapists will use whatever methods they usually use to make decisions regarding the frequency of therapy sessions (weekly, twice per week, every other week, etc) and whether to refer the adolescent to start an SSRI. If an adolescent is referred for medication management, the psychopharmacologist will follow the medication management procedures that they usually use and believe to be effective in clinical practice.

Drug/Device Handling:

The psychopharmacologist will give the adolescent a prescription for the SSRI that they will then fill with a licensed pharmacy.

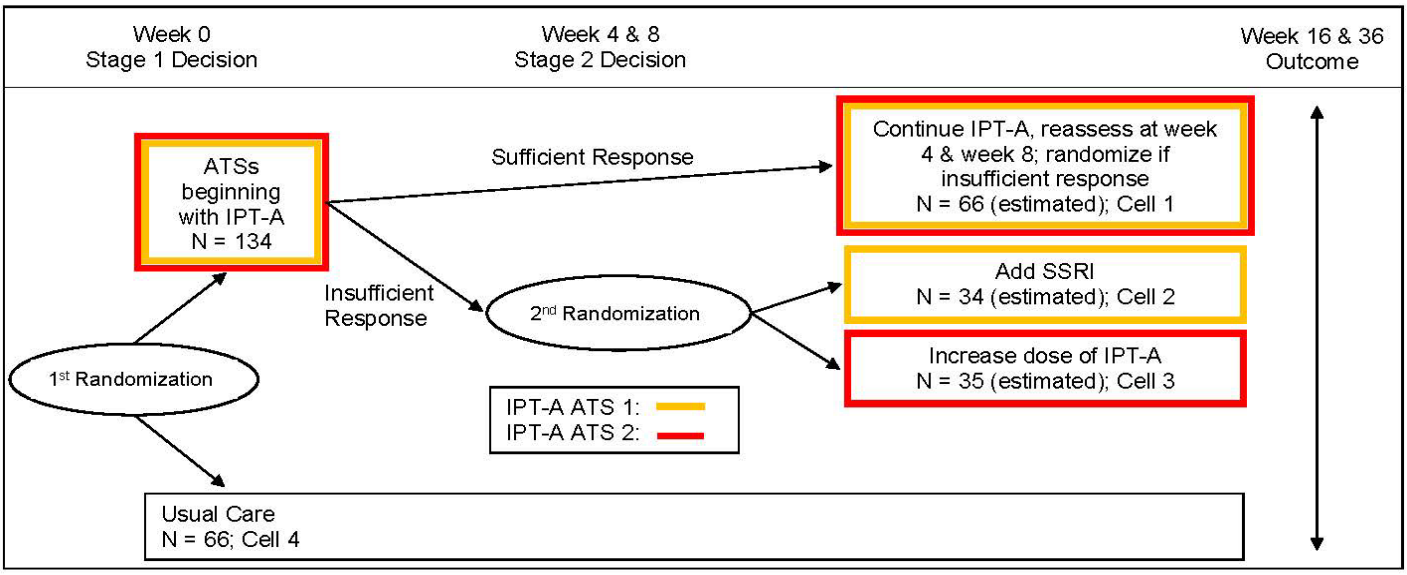
IND/IDE: N/A

Biosafety: N/A

## 5.0 Procedures Involved

Study Design:

Two hundred adolescents who present for treatment for depression at community mental health clinics (PrairieCare and Minnesota Mental Health Clinics) will be recruited to participate in a sequential multiple assignment randomized trial (SMART; see Figure 1). Subjects will be initially randomized using a 2:1 allocation ratio to IPT-A ATS or UC. Subjects randomized to IPT-A AST who are insufficient responders at week 4 or 8 will be re-randomized using a 1:1 allocation ratio to the addition of an SSRI or increased dose of IPT-A. Subjects will be block randomized using randomly permuted blocks of 2 and 4. The first randomization will be stratified by clinic site, CDRS-R (< 55 and ≥ 55), and CBQ strata (< 9 and ≥ 9).[108,112] The second randomization will be stratified by clinic site, HRSD (< 20 and ≥ 20), and CBQ strata (< 9 and ≥ 9). Assessments will be administered by evaluators who are blind to treatment condition at baseline and weeks 4, 8, 12, 16, and 36.




Study Procedures:

IPT-A Adaptive Treatment Strategies (IPT-A ATSs). Adolescents randomized to the IPT-A AST condition will begin IPT-A with an initial treatment plan of 12 weekly sessions. Therapists will be staff therapists already employed by PrairieCare and Minnesota community mental health clinics. Therapists are masters level clinicians (LPCC, LICSW, LP). Therapists will be trained and supervised in IPT-A and the AST procedures by Dr. Gunlicks-Stoessel (Project Director, Kristina Reigstad, PsyD, LP, may provide supervision at times when Dr. Gunlicks-Stoessel is not available. Dr. Reigstad has been previous trained in IPT-

A by Dr. Gunlicks-Stoessel). As part of treatment, therapists will administer the HRSD at weeks 1, 4, and 8. Therapists will enter the scores into a secure HIPAA-compliant web application (Research Electronic Data Capture; REDCap). REDCap will be programmed to calculate the percent change in HRSD from week 1 to week 4, and from week 1 to week 8, as well as the algorithm for specifying the stage 2 treatment decision. If the adolescent has demonstrated < 20% reduction on the HRSD at week 4, REDCap will trigger the randomized stage 2 treatment: increase dose of IPT-A or add SSRI. If the adolescent has demonstrated ≥ 20% reduction in depression on the HRSD at week 4, REDCap will trigger the therapist to inform the family that no change in treatment will be made and the adolescent will continue the initial treatment plan of 12 IPT-A sessions. If an adolescent who was a week 4 sufficient responder continues to be a week 8 sufficient responder (≥ 40% reduction in depression on the HRSD), REDCap will trigger the therapist to inform the family that no change in treatment will be made and the adolescent will continue the initial treatment plan of 12 IPT-A sessions. If an adolescent who was a week 4 sufficient responder becomes a week 8 insufficient responder (< 40% reduction in depression on the HRSD), REDCap will trigger the randomized stage 2 treatment: increase dose of IPT-A or add SSRI. If an adolescent misses the week 4 or week 8 session, the HRSD will be completed at the next attended session and the decision regarding stage 2 treatment will occur at that session. Adolescents randomized to increase IPT-A will receive an additional four IPT-A sessions scheduled twice a week (16 sessions total). Adolescents randomized to add SSRI will be referred to a psychopharmacologist to start an SSRI in addition to completing the remainder of their 12 IPT-A sessions.

Selective Serotonin Reuptake Inhibitors (SSRIs). Adolescents randomized to receive an SSRI at stage 2 will be prescribed an SSRI by a staff psychopharmacologist already employed by the mental health clinics. Psychopharmacologists will be psychiatrists and/or psychiatric nurse practitioners. They will receive training in the medication protocol from co-investigator, Kathryn Cullen, MD. Dr. Cullen will also provide quarterly consultation. Fluoxetine will be the first choice SSRI. Escitalopram will be the second choice. The psychopharmacologist may choose to select escitalopram first if clinically indicated when there is a previous history of intolerance to fluoxetine, based on family history or preference, and inability to achieve an adequate fluoxetine dose. Citalopram, fluvoxamine, and sertraline may also be selected first if clinically indicated, as above. The medication management protocol will follow standard clinical practices. Prior to initiation of the SSRI, all female patients will be asked, “Is it possible that you could be pregnant?” and “Have you recently or are you currently having any unprotected sex?”. If a female patient endorses either of these questions, they will be counseled on the risks of taking an SSRI and encouraged to practice safe sex practices. If the patient believes that she may be pregnant, she will be instructed to take a pregnancy test before beginning

medication. If a patient is pregnant, medication management will not be initiated. If a female adolescent who is taking an SSRI becomes pregnant over the course of the trial, her psychopharmacologist will provide council on the potential risks and benefits of continuing the medication. If the patient and psychopharmacologist decide to discontinue the medication, the patient can continue to receive IPT-A and continue to participate in the study assessments. Medication sessions will be scheduled weekly for the first two weeks, biweekly for the subsequent 6 weeks, and monthly thereafter. Sessions will include assessment of vital signs, adverse effects, safety, and symptomatic response. The medication dosing will follow published guidelines.[10,113] Psychopharmacologists will be advised to decrease the dose as necessary at any point to address tolerability problems. Adolescents will be asked to bring back the bottle of pills to each appointment to track adherence. _ENREF_10 _ENREF_113

***SSRI Titration Schedule***

| *Medication* | *Starting mg/d* | *Increments mg* | *Effective mg* | *Maximum mg* |
|---|---|---|---|---|
| *Citalopram* | *10* | *10* | *20* | *60* |
| *Fluoxetine* | *10* | *10–20* | *20* | *60* |
| *Fluvoxamine* | *50* | *50* | *150* | *300* |
| *Sertraline* | *25* | *12.5–25* | *50* | *200* |
| *Escitalopram* | *5* | *5* | *10* | *20* |

Usual Care (UC). Adolescents randomized to UC will receive care as usual, as described above in Section 4

Assessments. Assessments will be administered by independent evaluators who will remain blind to treatment condition. They will be required to have at least a Master's degree and one year experience administering clinical interviews, and they will be trained in the study measures by Dr. Gunlicks-Stoessel and Dr. Reigstad. Participants will consent to their assessment sessions being audio recorded. The recordings are for fidelity monitoring. Participants will not be able to opt out of the audio recording.

The baseline research assessment will take approximately 5 hours (split into two visits), the week 4 and week 8 assessments will each take approximately 2 hours, the week 12 assessment will take approximately one hour, and the week 16 and week 36 assessments will take approximately 3 hours each.

Saliva Collection. During each assessments point (Baseline, Week 4, Week 8, Week 16), a study staff member will provide the adolescent participant with written step-by-step instructions for the collection of a saliva sample using the Oragene DISCOVER saliva self-collection kit (DNA Genotek, Ottawa, ON, Canada, Catalog number OGR-500) and ask the participant to not eat, drink, smoke or chew gum for 30 minutes before giving a saliva sample. The total amount of saliva collected is approximately 2 milliliters (about half a teaspoon) and will take approximately 5 minutes to complete.

Nucleic Acid (DNA and RNA) Extraction. Collected saliva samples will be stored in the laboratory of Dr. Jeffrey R. Bishop at the University of Minnesota (516 Delaware Street S.E. Phillips-Wangensteen Building room B150 Minneapolis, MN 55455). Saliva samples will be processed for both DNA and RNA using the prepIT extraction kit following the manufacturer's standard protocol (DNA Genotek, Ottawa, ON, Canada, catalog number PT-L2P-5). Extracted DNA will be quantified by the Quant-iT™ PicoGreen™ dsDNA Assay Kit (Invitrogen, Waltham, MA USA, Catalog number P7589) using the Synergy HTX mult-imode plate reader (BioTek Instruments, Winooski, VT, USA). Extracted RNA will be quantified by the Quant-iT™ RiboGreen™ RNA Assay Kit (Invitrogen, Waltham, MA USA, Catalog number R11490) using the Synergy HTX mult-imode plate reader.

Genotyping and DNA methylation detection. DNA extracted from saliva specimens will be standardized to a working concentration of either 10ng/µl prior to genotyping or 25ng/µl prior to DNA methylation assessment. Targeted gene variants will be genotyped using either TaqMan SNP Genotyping assays and the Applied Biosystems 7500 Real Time PCR system (Applied Biosystems, Foster City, CA, USA), or Restriction Fragment Length Polymorphism (RFLP) performed by fragment analysis on the 3730 Genetic Analyzer (Applied Biosystems). Genome-wide scale genotyping will be performed using the Infinium PsychArray that includes 265,000 proven tag SNPs found on the Infinium Core-24 BeadChip, 245,000 markers from the Infinium Exome-24 BeadChip, and 50,000 additional markers associated with common psychiatric disorders (Illumina, San Diego CA, USA) or a comparable alternative depending on price and availability. For methylation detection studies, DNA extracted from saliva specimens will be bisulfite-converted using the EZ DNA Methylation Kit (Zymo Research, Irvine, CA, USA). Bisulfite-modified DNA will be PCR-amplified using primers designed to cover target gene regions for CpG site DNA methylation detection, and sequenced using the Illumina MiSeq system following a standardized protocol at the University of Minnesota Genomics Core facility (UMGC). Genome-wide methylation assessments will be performed using the Infinium MethylationEPIC BeadChip Kit (Illumina) (or comparable alternative) which interrogates over 850,000 methylation sites quantitatively across the genome at single-nucleotide resolution.

Gene Expression Studies. RNA extracted from saliva specimens will be standardized to a working concentration of 200ng/µl prior to gene expression analysis. Expression analysis of target genes will be performed using the following: 1) TaqMan® Gene Expression Assays and the Applied Biosystems 7500 Real Time PCR system (Applied Biosystems, Foster City, CA, USA), and 2) nCounter® expression panels (neuropathology, inflammation, immunology, and miRNA) and the NanoString nCounter Analysis System (NanoString

Technologies, Seattle, WA) available through the Univeristy of Minnesota Genomics Core Center (UMGC). Genome-wide gene expression analysis will be performed using a next-Generation sequencing approach of double-stranded cDNA generated by reverse-transcription of RNA, known as RNA-Seq, which has become the standard method for genome-wide gene expression analysis. Strand-specific RNA-Seq library preparation and NGS using the Illumina MiSeq System will be performed at the UMGC.

Demographic, Medical, and Social History

- Demographics Form collects information regarding demographics, family constellation, and school functioning.
- Medical History collects comprehensive medical and developmental information about the adolescent.
- NDA Information Form collects information regarding legal name (according to birth certificate) and municipality of birth, as is required to report for the NIMH data archive.
- Pronouns Information Form collects information regarding participants' preferred pronouns.
- Impact of COVID-19 assesses parents' and adolescents' perceptions of how COVID-19 has impacted their family's financial situation, stress, emotional well-being, physical well-being, and relationships and modes of communication with others.

Adolescent Psychiatric Symptoms & Diagnoses

- Beck Depression Inventory-II (BDI-II)[105] is a self-report measure that assesses the severity of depressive symptoms.
- Children's Depression Rating Scale-Revised (CDRS-R) [104] is a clinician-administered semi-structured interview conducted with adolescents and parents that assesses depressive symptoms.
- Clinical Global Improvement (CGI)[106] is used in clinical trials to track change in patients' clinical status with treatment.
- Children's Global Assessment Scale (C-GAS)[114] is used in clinical trials to track change in general (global) functioning for youth under age 18.
- Columbia Suicide Severity Rating Scale (C-SSRS)[115] is a clinician-administered standardized suicidal rating system that is based on definitions of suicidality derived from empirical findings on the phenomenology of suicidality and identified predictive and risk factors.
- Hamilton Rating Scale for Depression (HRSD)[99,116] is a clinician-administered semi-structured interview assessing depressive symptoms. It is widely used with adolescents.[117]
- Schedule for Affective Disorders and Schizophrenia for School-aged Children – Present and Lifetime Version (K-SADS-PL)[118] is a clinician-administered semi-

structured interview conducted with adolescents and parents that assesses present episode and lifetime history of DSM psychiatric diagnoses.

- Side Effects Form for Children and Adolescents[119] is a commonly used measure of treatment-related adverse events and side effects observed in children and adolescents receiving pharmacological treatment.

| Assessment | Informant | Base-line 1 | Base-line 2 | Wk 4 | Wk 8 | Wk 12 | Wk 16 | Wk 36 |
|---|---|---|---|---|---|---|---|---|
| **Demographic, Medical, and Social History** | | | | | | | | |
| Demographics | Parent Adolescent | | X | | | | | |
| Medical History | Parent | | X | | | | | |
| Preferred Pronouns | Adolescent | | X | | | | | |
| NDA Information | Parent | | X | | | | | |
| Impact of COVID-19 | Parent Adolescent | | X | X | X | X | X | X |
| **Adolescent Psychiatric Symptoms & Diagnoses** | | | | | | | | |
| BDI-II | Adolescent | | X | X | X | X | X | X |
| CDRS-R | Adolescent Parent | X | | X | X | X | X | X |
| CGI | Adolescent | | X | X | X | X | X | X |
| C-GAS | Adolescent | X | | X | X | X | X | X |
| C-SSRS | Adolescent | X | | X | X | X | X | X |
| HRSD* | Adolescent | | X | X | X | | | |
| K-SADS-PL | Adolescent Parent | X | X | | | | X | X |
| Side Effects | Adolescent | | X | X | X | X | X | |
| **Interpersonal Processes** | | | | | | | | |
| CBQ | Adolescent Parent | | X | X | X | X | X | X |
| IPPA | Adolescent | | X | X | X | X | X | X |
| P-A Conflict Task | Adolescent Parent | | X | X | X | | X | |
| **Candidate Treatment Moderators** | | | | | | | | |
| ET | Adolescent Parent | | X | X | X | X | X | X |
| SASC | Adolescent | | X | | | | | |
| SOCQ | Adolescent | | X | X | X | | | |
| **COVID-19 Measures** | | | | | | | | |
| Impact of COVID-19 | Adolescent Parent | | X | X | X | X | X | X |
| | | | | | | | | |
| **Implementation-Focused Process Evaluation** | | | | | | | | |
| ATA | Adolescent Parent | | X | | | | X | |
| CSQ-8 | Adolescent Parent | | | | | | X | |
| Satisfaction with Telehealth | Adolescent Parent | | | | | | X | |
| ATA-T | Therapists | | | | | | X | |

| | | | |
|---|---|---|---|
| Staff Background Information | Therapists & Clinic staff | | Therapists: At start of study participation<br>Staff: At the end of the study |
| EBPAS-36 | Therapists & Clinic staff | | Therapists: at start and end of study participation<br>Staff: At the end of the study |
| ORCA | Therapists & Clinic staff | | Therapists: at end of study participation<br>Staff: At the end of the study |
| Implementation interview | Therapists & Clinic staff | | Therapists: at end of study participation<br>Staff: At the end of the study |

*completed as part of treatment; not a research measure

Interpersonal Processes

- Conflict Behavior Questionnaire (CBQ)[120] is a self-report measure that assesses parent-child communication, conflict, and relationship functioning. The CBQ will be completed by adolescents and parents.
- Inventory of Parent and Peer Attachment (IPPA_ENREF_107)[107] is a self-report measure of adolescents' degree of mutual trust; communication quality; and anger and alienation with their mother, father, and a close peer.

Parent-Adolescent Conflict Task. Issues Checklist (IC)[108] consists of 50 typical topics of parent-adolescent conflict. For each issue, adolescents and parents indicate whether it was a topic of discussion during the last month and the intensity of the discussion. It has frequently been used as a means of identifying a topic for observational assessments of parent-adolescent interactions. Conflict Negotiation Task. Using the IC, a topic that both the parent and adolescent rated as a source of frequent and moderately heated discussions will be identified. Parents and adolescents will spend 15 minutes describing the issue and attempting to resolve the problem.[121] Participants will consent to their conflict discussion being videotaped. Participants will not be able to opt out of the video recording. In response to Covid-19, video recording will be completed using Zoom, a HIPAA-compliant web-based platform. The option of recording to the cloud is disabled, and instead the recording will save to the research staff's hard drive. The recording will then be uploaded to Box Secure Storage and promptly deleted off the hard drive to maintain HIPAA compliance. Video-Recall Procedure.[109,110] At Baseline and Week 16 appointments, adolescents and parents will view the videotape twice. First they will rate on a 5-point Likert scale the extent to which their own behaviors were supportive, conflictual, humorous, submissive (giving in), and sarcastic. After each 15-second portion of the video, a computer will pause the tape for 15 seconds, and the adolescents and parents will complete the rating scales, considering the full 15-second segment of the discussion. They will rate 32 segments, for a total of 8 minutes of interaction. Subsequently, parents and adolescents will view the same 8-minute portion of videotape again and repeat the procedure, this time rating the extent to which the behaviors of the other person indicated support, conflict, humor, submission, and misunderstanding. Adolescents' and parents' ratings for themselves and for each other will be separately aggregated for a total score for each behavior. At

Baseline, Week 4, Week 8, and Week 16 appointments, adolescents and parents will also complete a shortened version of this task. They will rate on a 5-point Likert scale the extent to which their own behaviors were supportive, conflictual, humorous, submissive (giving in), and sarcastic, considering the entire duration of the conflict discussion. Subsequently, they will then repeat the procedure this time rating the extent to which the behaviors of the other person indicated support, conflict, humor, submission, and misunderstanding, considering the entire duration of the conflict discussion. Electrocardiograms.

Candidate Treatment Moderators

- Expectations for Treatment (ET)[122] assesses adolescents' and parents' expectations of how successful and suitable they think their treatment will be.
- Sociotropy-Achievement Scale for Children (SASC)[123] is a self-report measure that assesses sociotropy (the degree to which one values his/her interpersonal relationships) and achievement-orientation (the degree to which one values achievement and goal attainment).
- Stages of Change Questionnaire (SOCQ)[124,125] is an assessment of an individual's awareness of life problems and readiness to make changes in their behavior to address these problems. It provides scores for the four stages of readiness to change: precontemplation, contemplation, action, and maintenance. It has been adapted for use with adolescents.[124]

Cost Effectiveness

- Clinic Record Review. All treatment providers will keep detailed records on study patients, following their clinic's protocol. Records will include type of treatment (psychotherapy, medication management), treatment duration, session attendance, no-shows/cancellations, telephone contacts, and other data required for service and cost documentation.
- The Child and Adolescent Services Assessment (CASA)[126] is a reliable and valid measure that will be used to assess services received by the youth during and following the intervention.

Treatment Fidelity and Characterization

- Recordings of Therapy Sessions. Participants will consent to their treatment sessions being recorded. The recordings are for fidelity monitoring and to code and characterize the usual care condition. Participants will not be able to opt out of the recording.
- ATS Implementation Checklist is an ATS fidelity measure that includes a checklist of procedures to be implemented (administers the HRSD, communicates the correct stage 2 treatment, etc.) and a likert scale score of effectiveness in communicating the stage 2 treatment (e.g. effectively addresses questions, "sells" the treatment to increase engagement). It is completed based on the audiotape of each therapy session.

- IPT-A Supervision Checklist[127] is a IPT-A fidelity rating scale based on the audiotape of each therapy session.
- Therapy Process Observational Coding System for Child Psychotherapy-Revised Strategies Scale (TPOCS-RS)[128] is a psychotherapy coding system. It consists of five theory-based subscales (Cognitive, Behavioral, Psychodynamic, Family, and Client-Centered) along with eight items that represent interventions that are considered to play a meaningful role in child therapy but are not associated with a specific subscale (e.g., homework). The TPOCS-RS has been shown to have strong reliability and validity.[129]
- Psychiatric Medication Log tracks all psychiatric medications received by the adolescent during the course of the study.

Implementation-Focused Process Evaluation:

- Adaptive Treatment Attitudes (ATA)[38] assesses adolescents' and parents' attitudes regarding changing the adolescents' treatment plan and the type of treatment change for insufficient responders.
- Client Satisfaction Questionnaire (CSQ-8)[130] is a self-report instrument used to assess adolescents' and parents' satisfaction with treatment.
- Satisfaction with Telehealth assesses adolescents' and parents' satisfaction with receiving services via telehealth. It was adapted from the Telehealth Usability Questionnaire (TUQ).
- Adaptive Treatment Attitudes – Therapists (ATS-T)[38] assesses therapists' attitudes regarding changing the adolescents' treatment plan and the type of change to the treatment plan for insufficient responders.
- Clinic Staff Background Information assesses previous work experience, educational background, demographic characteristics, and approach to therapy.
- and attitudes about different treatment approaches.
- Evidence-Based Practice Attitude Scale-36 (EBPAS-36)[131] is a brief and pragmatic measure of attitudes to evidence-based practices.
- Research Team Observational Log will document interactions that research staff have with patients, treatment providers, other clinic staff, or members of the leadership that provide information regarding attitudes about the ATSs or perceived barriers or facilitators to their adoption, implementation, and maintenance.
- Post-Treatment Interviews with Treatment Providers and Leadership will include assessment of opinions regarding the intervention and the impact of the intervention on the clinic, providers' interactions with patients, and staff workload. They will be asked about barriers and facilitators to adopting and implementing the intervention as part of the clinic's standard care. Suggestions will be elicited regarding resources, tools, and training that would be needed to deliver the intervention and integrate it into regular practice.
- Organizational Readiness to Change Assessment (ORCA) Evidence Scales[132] assesses clinic staff opinions of the intervention based on their perception of its

research evidence, their clinical experience, and their perception of patient attitudes. It also assesses their perceptions of colleagues' opinions.

- ORCA Context Scales[132] assesses clinic staff perceptions of the organization's leadership culture, staff culture, leadership feedback, readiness to change, and resources to support practice changes.

Follow-Up: Assessment schedule and measures are described above.

Individually Identifiable Health Information: This research will involve the use of individually identifiable health information. We will have all participants complete a HIPAA authorization form. We will follow UMN Privacy Office Policies

Use of radiation*:* N/A

Use of Center for Magnetic Resonance Research*:* N/A

## 6.0 Data and Specimen Banking

Storage and Access: All data resulting from the proposed project will be shared via the National Database for Clinical Trials (NDCT). Qualified researchers can request access to shared data in NDCT. Researchers can view summary-level data, or can request access to query and download subject-level data. Researchers who would like to access shared must complete a Data Use Certification (DUC) form and submit it for review by a Data Access Committee. There are three criteria researchers must meet to be eligible to request access: (1) the researcher must have a research-related need to access the data, (2) the researcher must be associated with an NIH-recognized research institution, defined as an institution registered in the NIH electronic research administration system (eRA Commons) and have the approval of an authorized signatory official of that institution, and (3) the researcher's institution must have an active Federalwide Assurance (FWA.)

Biological specimens: All biological specimens (saliva, DNA, and RNA) collected through this protocol will be stored in the laboratory of Dr. Jeffrey R. Bishop at the University of Minnesota (516 Delaware Street S.E. Phillips-Wangensteen Building room B150 Minneapolis, MN 55455). All specimens will be labeled and stored with a de-identified study specimen number, not with any personal or protected health information.

Data: All data will be de-identified via the use of a Global Unique Identifiers (GUIDS) and shared. We will work with the NIMH to create data dictionaries that are relevant to the research.

Release/Sharing: The researchers will work with the NIMH to determine an appropriate schedule for sharing the data with the research community.

## 7.0 Sharing of Results with Participants

No individual results will be shared with participants or others (e.g., participants' primary care physicians).

## 8.0 Study Duration

- Duration anticipated for an individual participant's participation in the study: 36 weeks
- Duration anticipated to enroll all study participants: 4 years
- Duration anticipated to complete all study procedures and data analysis: 5 years

## 9.0 Study Population

Adolescent Inclusion Criteria:

1) Male and female adolescents (ages 12-18)

2) meet DSM-V criteria for a primary diagnosis of Major Depressive Disorder, Persistent Depressive Disorder, or Depressive Disorder NEC (based on the K-SADS[118]);

3) demonstrate symptoms of depression (CDRS-R[104] $\geq$ 36); and

4) demonstrate impairment in functioning (CGAS[114] $\leq$ 65) during a baseline evaluation conducted by an IE.

Adolescent Exclusion Criteria:

1) Non English-speaking

2) Meet criteria for bipolar disorder, psychosis, anorexia nervosa (other eating disorders will be included), substance use disorder (substance use will be included), autism spectrum disorder, or intellectual disability disorder (based on school placement information).

3) Depressed adolescents who are actively suicidal with a plan and/or intent who are assessed to need a higher level of care than outpatient treatment due to safety risk will be referred for appropriate level of stabilization (inpatient, partial hospitalization, intensive outpatient). Once stabilized, the adolescent can be re-evaluated for eligibility to participate in the study.

4) Adolescents will be excluded if they are already receiving treatment for depression or if they are taking medication for a psychiatric diagnosis other than ADHD. Adolescents with comorbid ADHD who are on a stable dose of stimulant medication (> 3 months) will be eligible. Interested families with adolescents currently taking psychiatric medication may, if desired, undergo a medication washout process to participate in the study. With the approval and oversight of their prescribing clinician, adolescents may choose to stop their medication. The prescribing clinician will determine with the families how to best wean off the medication. After 2 weeks completely off the medication, adolescents may be re-

considered for study eligibility. If the adolescent is taking fluoxetine, the required washout period will be 3 weeks rather than 2 weeks.

Parent/Caregiver Inclusion Criteria:

1) Parent/caregiver of an adolescent enrolled in the study

Parent/Caregiver Exclusion Criteria:

1) Non English-speaking

Therapist Inclusion Criteria:

1) Therapist at PrairieCare or Minnesota Mental Health Clinics who agrees to provide psychotherapy to an adolescent enrolled in the study

Clinic Staff Inclusion Criteria:

1) Treatment providers, other clinic staff, and members of the leadership team at PrairieCare and Minnesota Mental Health Clinics

Screening:

PrairieCare has two screening pathways:

(1) PrairieCare offers free psychiatric needs assessments for families who are unsure if they are in need of services or are unsure what level of service is needed (e.g. outpatient, partial hospitalization, inpatient). If the clinician determines that the adolescent has a depression diagnosis and outpatient level of care is appropriate, the clinician will provide information about the study to the adolescent and parents.

(2) Some families call PrairieCare's outpatient clinic directly to initiate outpatient services. If families' initial call with an intake coordinator is regarding an adolescent aged 12-18 years, the intake coordinator will inform the families that they can schedule a screening appointment with the University of Minnesota team to obtain a diagnostic evaluation and, if eligible, hear about participation in the study as an option.

Minnesota Mental Health Clinics has two screening pathways:

(1) Families who call the clinics to initiate outpatient services speak with an intake coordinator to schedule an appointment. If families' initial call with an

intake coordinator is regarding an adolescent aged 12-18 years, the intake coordinator will provide information about the study to the family.

(2) Therapists in the clinic who meet with a family with an adolescent (age 12-18) for an intake and/or ongoing therapy can provide information about the study to the family.

Additional screening pathway for both sites:

Some families will be directed to the study through recruitment sources other than PrairieCare and Minnesota Mental Health Clinics. Families who are referred from other organizations that serve youth (e.g., pediatric clinics) will complete a permission to contact form which will be faxed to the research team, indicating parents' permission to be contacted by research staff. Parents may either (a) participate in a structured telephone screen with study staff that asks about mood, medical history, and current and prior treatment. If a parent completes the phone screen and the adolescent appears eligible, they will be asked to meet with an independent evaluator (IE) to learn more about the study, provide consent/assent, and complete the baseline assessments to determine eligibility. Or (b) schedule an in-person screening appointment with the University of Minnesota team to obtain a diagnostic evaluation and, if eligible, hear about participation in the study as an option.

If the parent opts to schedule the screening appointment, parent and adolescent will complete screening consent/assent forms. They will then complete the "assessment of current symptoms" in the screening module of the K-SADS-PL, as well as any supplements that may determine eligibility/ineligibility if symptoms are endorsed during the screening module (affective, psychotic, substance use, eating disorders, and autism spectrum disorders supplements). Parent and adolescent will also complete the CDRS-R, C-GAS, and C-SSRS, as well as the Brief Screen Additional Information form. If parent and adolescent are deemed eligible, study staff will describe the study. If the family is interested in participating in the study, study staff will proceed to schedule them for the Baseline visit to complete the study consent and remaining Baseline measures. If families are ineligible or are eligible and decide not to participate in the study, they will be referred to services at PrairieCare, Minnesota Mental Health Clinics, or other services. Based on the needs of patients and availability of providers, some families will be directed to study treatment options outside of PrairieCare and Minnesota Mental Health Clinics.

Reassessment of eligibility if there is a delay in starting treatment:

If there is a > 2 week, but < 6 week delay between the eligibility evaluation and starting treatment, the following measures will be re-administered to re-assess eligibility and re-establish baseline scores, as the measures only capture symptoms in the previous 1-2 weeks: CDRS-R, BDI-II, CGI.

If there is a > 6 week delay between the eligibility evaluation and starting treatment, all baseline measures will be re-administered.

If an adolescent is found to be ineligible at re-assessment, referrals to PrairieCare, Minnesota Mental Health Clinics, or other services will be made, as described above.

## 10.0 Vulnerable Populations

- ☒ Children
- ☐ Pregnant women/Fetuses/Neonates
- ☐ Prisoners
- ☒ Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders
- ☐ Approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.
- ☐ Disadvantaged in the distribution of social goods and services such as income, housing, or healthcare
- ☐ Serious health condition for which there are no satisfactory standard treatments
- ☐ Fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior)
- ☐ Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research
- ☐ Undervalued or disenfranchised social group
- ☐ Members of the military
- ☐ Non-English speakers
- ☐ Those unable to read (illiterate)
- ☐ Employees of the researcher
- ☐ Students of the researcher
- ☐ None of the above

Adults lacking capacity to consent and/or adults with diminished capacity to consent:

The study sample includes adolescents up through 18 years of age. The sample consists solely of adolescents because adolescence has been identified as a critical period for the treatment of depression, given that it is characterized by a significant rise in the rates of depressive symptoms and diagnoses.[133]

This population represents the least degree of impairment compatible with the aims of this study. We are not enrolling participants during hospitalizations. We are also not enrolling adolescents who are actively suicidal with a plan and/or intent who are assessed to need a higher level of care than outpatient treatment. Once stabilized, the adolescent can be re-evaluated for eligibility to participate in the study.

- The MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) will be used to assess capacity to consent.
- If we encounter a participant 18 years of age or older with diminished/fluctuating capacity to consent, we will ask this participant to sign the assent form and their LAR to sign the main consent form.
- Criteria for study withdrawal are described below in section 13
- Procedures to minimize risks are described below in section 14

Additional Safeguards

Parents will provide consent for their child to participate and adolescents will provide assent. This research team has considerable experience and expertise conducting research with adolescents and will train all research staff in the ethical conduct of research with adolescents.

## 11.0 Local Number of Participants

Local Number of Participants to be Consented: We expect to consent approximately 240 adolescents and parents/caregivers in order to reach a target sample of 200 participants who meet eligibility criteria to enroll in the trial. We expect to consent approximately 50 Minnesota mental health clinic staff members.

## 12.0 Local Recruitment Methods

Recruitment Process:

Recruitment from PrairieCare:

(1) PrairieCare offers free psychiatric needs assessments for families who are unsure if they are in need of services or are unsure what level of service is needed (e.g. outpatient, partial hospitalization, inpatient). If the clinician determines that the adolescent has a depression diagnosis and outpatient level of care is appropriate, the clinician will provide information about the study to the adolescent and parents. If families are interested in learning more about the study, clinic staff will document permission to be contacted by research staff on a "consent to contact" form that will be faxed to the research team. The clinic staff will also have the option to complete the "consent to contact" form via a link to a secure, HIPAA compliant, REDCap database.

(2) Some families call PrairieCare's outpatient clinic directly to initiate outpatient services. If families' initial call with an intake coordinator is regarding an adolescent aged 12-18 years, the intake coordinator will inform the families that they can schedule a screening appointment with the University of Minnesota team to obtain a diagnostic evaluation and, if eligible, hear about participation in the study as an option. If families are interested in learning more about the study, clinic staff will document permission to be contacted by research staff on a "consent to contact" form that will be faxed to the research team. The clinic staff will also have the option to complete the "consent to contact" form via a link to a secure, HIPAA compliant, REDCap database.

Recruitment from Minnesota Mental Health Clinics:

(1) Families who call the clinics to initiate outpatient services speak with an intake coordinator to schedule an appointment. If families' initial call with an intake coordinator is regarding an adolescent aged 12-18 years, the intake coordinator will provide information about the study to the family. If families are interested in learning more about the study, the intake coordinator will document permission to be contacted by research staff on a "consent to contact" form that will be faxed to the research team. The intake coordinator will also have the option to complete the "consent to contact" form via a link to a secure, HIPAA compliant, REDCap database.

(2) Therapists in the clinic who meet with a family for an intake and/or ongoing therapy can provide information about the study to the family. If families are interested in learning more about the study, therapists will document permission to be contacted by research staff on a "consent to contact" form that will be faxed to the research team. The therapist will also have the option to complete the "consent to contact" form via a link to a secure, HIPAA compliant, REDCap database.

Additional recruitment methods:

(1) The research team will recruit from pediatric clinics, mental health clinics, schools, and community centers that are proximal to PrairieCare and Minnesota Mental Health Clinics (sites which may serve individuals that are likely to seek services at PrairieCare or Minnesota Mental Health Clinics). At sites that serve low income and/or minority populations, the team will also offer to provide psychoeducational workshops for treatment providers and families who are interested in learning more about adolescent depression and its treatment. Information about the study will be provided. This effort will ensure a more diverse, representative sample.

(2) Study information will also be on display at the UMN Department of Psychiatry recruitment display board.

(3) Posters will be posted around the Twin Cities metro area in businesses and public spaces.

(4) Advertisements will be aired on local radio stations and published on digital platforms.

Source of Participants: Adolescents seeking treatment for depression, as described above.

Identification of Potential Participants: See 'Recruitment Process' Section above.

Recruitment Materials: PrairieCare and Minnesota Mental Health Clinic staff will use the study brochure and Permission to be Contacted form to introduce the family to the study. Research staff will use the introductory informational letter to offer to provide psychoeducational workshops at pediatric clinics, mental health clinics, schools, and community centers that serve low income and/or minority populations. A psychoeducational article will be given with pediatric clinics, mental health clinics, schools, and community centers to share with their clients. The Department of Psychiatry recruitment display board will include contact cards and a poster briefly detailing the study. Contact cards and study posters or postcards will also be used for recruitment at PrairieCare, Minnesota Mental Health Clinics, and pediatric clinics, mental health clinics, schools, and community centers that are proximal to PrairieCare and Minnesota Mental Health Clinics. Posters with removable contact information tabs will be posted around the Twin Cities area in businesses and public spaces. Radio ads will be aired on local stations with study team contact information. Advertisements with an informative graphic and a link to the study website will also be published on social media and digital platforms (e.g., Facebook, Craigslist). The study website will be hosted on Discovery Partners.

Individuals who want to be contacted about the study will complete contact information via a link to a secure, HIPAA compliant, REDCap database. Only the study coordinator and Principal Investigator, Meredith Gunlicks-Stoessel, will have access to the secure database. A link and quick response code (QR) for the contact form will be used on paper and digital materials. Individuals will provide their name and a preferred method of communication, such as an email address and/or phone number. We will use the approved screening script and form when contacting potential participants.

Payment: Adolescents will be compensated $70 for the baseline, week 4, week 8, week 16, and week 36 assessments, and $25 for the week 12 assessment. Parents will be compensated $30 for the baseline, week 4, week 8, week 16, and week 36 assessments, and $15 for the week 12 assessments. Total compensation for adolescent participation in the study will be up to $375. Total compensation for parents will be up to $165. If a particular assessment is deemed too time-intensive for completion in a single visit, it may be preemptively split into two appointments; the allocated payment for that assessment will be split evenly and distributed accordingly after the completion of each partial visit (i.e., an assessment with a compensation value of $70 would be distributed in two $35 payments). If research interviews still exceed the scheduled time and an additional

appointment is required to complete the interview, participants (either parents or adolescents) will be compensated an additional $20. Therapists will be paid $20 for completing measures at the start of their participation in the study and $40 for completing the measures at the end of their participation in the study. Clinic staff will be paid $40 for completion of measures.
Payment will be made using a pre-paid debit card called Greenphire ClinCard. This system functions like a bank debit card; participants will receive a debit card, and each time they receive a payment for participation in this study, the money will be added to the card after each completed visit.

Participants may use this card at any store that accepts MasterCard or can use a bank machine to remove cash. There may be fees drawn against the balance of the card for cash withdrawals (ATM use) and inactivity (no use for 3 months). Participants will be provided with the ClinCard Frequently Asked Questions information sheet that answers common questions about the debit card. They will also receive letters with additional information on how they can use these cards and who to call if questions arise.

The debit card system is administered by an outside company. The company, Greenphire, will be given participant names. This information will be used only as part of the payment system. This information will not be used for any other purposes and will not be given or sold to any other company. Greenphire will not receive any information about participants' health statuses or the study in which they are participating.

## 13.0 Withdrawal of Participants

Withdrawal Circumstances: Five conditions that may lead to a decision to terminate treatment prematurely are: (a) the adolescent's primary problem changes during treatment in a way that warrants changes in treatment priority (e.g., adolescent begins to use dangerous drugs); (b) parent and/or adolescent request a change of treatment focus or approach; (c) evidence of a deterioration with treatment; (d) evidence of a non-response to treatment at week 8 or week 12 evaluation time points; or (e) evidence of serious suicide risk.

An Independent Safety Monitor (ISM) will provide independent clinical consultation to the study team and treating clinicians, particularly in situations where there are concerns about the appropriateness of the subject continuing in the trial in the assigned arm of the treatment studies: 1) a suicide attempt, 2) serious suicidal ideation (with a plan) and refusal to contract for safety, 3) psychiatric hospitalization, 4) possible need for psychiatric hospitalization, 5) significant worsening of depressive or other clinical symptoms (CDRS-R > 76 or CGI improvement score > 5), 6) a non-response to treatment (CGI improvement score = 4 at week 8 or week 12), and 6) the need for alternative treatment outside of

protocol. Adolescents will be removed from the study **treatment** immediately following formal review if the ISM deems that the subject requires treatment outside of study protocols or if the treatment provided in the study is contraindicated.

Participants will not be withdrawn from the study **assessments** unless they withdraw consent or unless the ISM deems that continued participation in the assessments is causing harm to the participant.

Withdrawal Procedures: Participants who are withdrawn from the study treatment will be referred for alternative treatment at PraireCare, Minnesota Mental Health Clinics, or in an alternative community setting. Participants can continue to participate in the assessment procedures if they continue to provide consent/assent and the ISM deems participants safe to continue in the assessments. Data from the medical record regarding ongoing treatment (as described above in Section 5 above) will continue to be collected unless the parent withdraws consent.

Termination Procedures: Participants and the treating providers will be informed of termination within 24 hours following ISM review. Data will continue to be used after termination.

## 14.0 Risks to Participants

Foreseeable Risks: (1) During the assessments, subjects (adolescents and parents) could become upset, angry, or sad when completing the assessments. (2) During the interventions, feelings could arise that are upsetting to the participating individuals (adolescents and parents) and could lead to temporary feelings of anger, sadness, or being upset. (3) Adolescents could experience suicidal ideation or a deterioration with treatment. (4) Adolescents randomized to receive SSRI treatment could experience adverse effects of medications. While SSRIs are generally well tolerated, side effects do occur. The most commonly reported side effects are: nausea, tremor, overstimulation, headache, and gastrointestinal symptoms. There is also some indication that some children treated with antidepressant medications are at elevated risk for suicidal ideation and behavior.[134] (5) Risk of identifying adolescent abuse/maltreatment during an assessment or treatment session. Risks 2-5 will not be different than risks normally seen in standard clinical practice. Additional risks include the potential risk of loss of confidentiality.

Protections Against Risk:
Risk of becoming upset during the assessment. All clinical measures will be conducted by experienced, trained IEs. The IEs will be master's level clinicians. The PI and study Project Director, Kristina Reigstad, PsyD, LP, will provide detailed training and supervision to the IEs in the administration of all measures. In the instance of any adolescent or parent becoming upset when completing any

of the measures, including the parent-adolescent conflict negotiation task, the IE will attempt to debrief and council the adolescent or parent. Parents and adolescents who are upset following the conflict negotiation task will also be offered the opportunity to take a break before completing other assessments. If needed, the IE will contact the PI or Dr. Reigstad, who will assess the situation, and as necessary, will counsel the adolescent and/or the parent.

Risk of becoming upset during the intervention. UC and IPT-A therapists will be masters or doctoral level clinicians (LPCC, LICSW, LP) currently employed by PrairieCare or Minnesota Mental Health Clinics. Pharmacotherapy will be delivered by psychopharmacologists (child psychiatrists and nurse practitioners) also already employed by PrairieCare or Minnesota Mental Health Clinics. Treatment providers will handle all clinical issues in the way they are generally handled at PrairieCare or Minnesota Mental Health Clinics. At PrairieCare, the Chief Psychotherapy Officer and the Chief Medical Officer will oversee the services by supervising and providing support and assistance to the treatment providers implementing the interventions. At Minnesota Mental Health Clinics, oversight will be provided by the Clinic Director. Furthermore, additional strategies will be implemented to minimize risk to research subjects. First, the IPT-A therapists will be trained and supervised by the PI. Second, the PI will closely monitor subjects throughout the course of treatment and will review all the assessments to identify any adolescent who may be at-risk.

Risk of suicide or deterioration with treatment. Rescue procedures will follow the standard suicide prevention procedures as outlined in the AACAP Practice Parameters on Suicidal Behavior,[135] including risk assessment, identification and modification of precipitants, and contracting for safety. All study staff will be trained to follow these parameters. Subjects will be educated about depression and signs of suicidal crisis. Subjects will receive PrairieCare's or Minnesota Mental Health Clinic's 24 hour on-call phone number. Subjects may fail to appear for treatment or assessment appointments. We will obtain locator information and obtain permission to contact three identified family members or friends in the event of a no-show for an assessment or therapy appointment. All subjects will be closely monitored with regard to suicidality on a frequent and regular basis (during treatment sessions and IE-administered assessments). Subjects who show deterioration in depression, mania, psychosis, or level of suicidality will be monitored closely. Subjects who are at risk may need to be psychiatrically hospitalized. If the treatment provider or IE is concerned about current suicide risk, the provider will follow the procedures that are consistent with the standard suicide prevention procedures as outlined in the AACAP Practice Parameters on Suicidal Behavior. The provider or IE will discuss these cases with the clinic leadership at the respective clinics, as well as the PI. Based on the information from various sources, the provider, PI, and clinic leadership at the respective sites will evaluate suicide risk and decide what level of care is sufficient. Subjects will be referred for

hospitalization if: a) his/her condition is unstable-as manifested by suicidal ideation with inability to agree to a safety plan, psychosis, mania, rapid cycling or mixed state; and b) there is a lack of sufficient environmental support and structure to guarantee the subject's safety.

For adolescents who are assessed to be safe to go home and are not referred for hospitalization, a safety plan will be established in collaboration with the subject and parents. The safety plan will include the adolescent's/parent's commitment to utilize a list of strategies that can help keep the adolescent safe in a suicidal crisis. The strategies will be individualized to each adolescent. The adolescent's safety plan will include: (a) strategies that the adolescent can employ with the help of others (adult that the adolescent can contact), and (b) strategies that the adolescent can use by him/herself without the help of others (emotion regulation skills). The parent's safety plan will include strategies that the parent can use to keep the adolescent safe. The parent's safety plan will also include calling 911 or going to the Emergency Room should any safety concerns arise, and will include procedures for limiting the adolescent's access to means of self-harm (e.g., medications, knives).

Also, as described in Section 13, an ISM will provide independent clinical consultation to the study team and treating clinicians, particularly in situations where there are concerns about the appropriateness of the subject continuing in the trial in the assigned arm of the treatment study. The adolescent will be removed from the study treatment if the ISM deems that the subject requires treatment outside of study protocols or if the treatment provided in the study is contraindicated.

Risk of side effects with SSRIs. While SSRIs are generally well tolerated, side effects do occur. Safety of the medication treatment will be monitored closely. The psychopharmacologists will be able to contact Dr. Cullen with any concerns or questions. The psychopharmacologists will review with families the following potential SSRI-related adverse events: gastrointestinal complaints (nausea, pain, diarrhea, and constipation) (frequency: 4-29%), dizziness (frequency 2-11%), allergic reactions (frequency: rare), increased anxiety or irritability(frequency: 3-15%), increased activation/restlessness (frequency: 2%), sleep changes (increased or decreased) (frequency: 5-30%), sexual side effects (frequency: 1-11%), appetite changes (increased or decreased) (frequency: 4-17%), unusual thoughts (frequency: rare), sweating (frequency: 2-9%), fatigue (frequency: 5-17%), suicidal ideation/attempts/and or behaviors (frequency: 4%). In addition to these issues, the psychopharmacologists 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. Adolescents will be instructed to call the treatment provider with any concerns. PrairieCare and Minnesota Mental Health Clinics have a 24 hour on-call service for urgent matters that develop outside of regular business hours.

To monitor potential risks, clinicians will carefully assess for any significant changes in mood, thinking, behaviors, physical symptoms, and suicidality, especially early in treatment. 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. Also, if a patient shows a worsening of symptoms, including suicidality, or develops exclusionary criteria described above, rescue procedures described above will be implemented and the patient will be evaluated by the ISM who will follow the procedures described above.

Risk of identifying adolescent abuse/maltreatment. The PI and Dr. Reigstad will provide training to the project staff in requirements and procedures for following up on and collecting information about child maltreatment. In any case where the possibility of maltreatment arises, the project staff involved will collect the information and will immediately confer with the PI or Dr. Reigstad, and mandated reporter requirements will be followed closely. The research team will also discuss these cases.

Risk of loss of confidentiality. The PI will emphasize the critical importance of subject confidentiality in the training of all project staff, and will reiterate this point as opportunities arise in handling of such material. All interviews and therapy sessions will take place in private rooms. All off-site communication between research staff and participants will occur by telephone or by email using the University's email encryption system to ensure security. At two points in the study participants will be given the option to request that the research team does *not* send encrypted emails using the University encryption system using a request form for communication via unencrypted email. The first opportunity to request unencrypted email communication will occur at first contact of interest with study participation. The second opportunity will occur during the consent meeting. Both opportunities have unencrypted email authorization forms collected via REDCap for electronic signatures. This form will disclose risks of communicating via unencrypted email and will require a participant signature to take effect. Participants will also be given the option to request that the research team uses text messaging to schedule and confirm appointments using a consent for text message correspondence form. This form will disclose risks of and parameters for communicating via text message and will also require a participant signature to

take effect. Text messages will only be sent from a password-protected university-owned device. In order to safeguard the confidentiality and security of data files, participants (adolescents and parents) will be assigned a coded identification number that will be used on all datacollection measures, including biological specimens. 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 subject ID numbers will be the only unique piece of information linking the data files to the consent file. 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. Genetic and epigenetic information will be for research purposes only and will not be included in participants' medical records. Genetic and epigenetic data obtained from this study will be de-identified by the use of subject ID numbers.

Data for this study will be entered into a REDCap database, which uses a MySQL database via a secure web interface with data checks used during data entry to ensure data quality. REDCap includes a complete suite of features to support HIPAA compliance, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. The MySQL database and the web server will both be housed on secure servers operated by the University of Minnesota Academic Health Center's Information Systems group (AHC-IS). The servers are in a physically secure location on campus and are backed up nightly, with the backups stored in accordance with the AHC-IS retention schedule of daily, weekly, and monthly tapes retained for 1 month, 3 months, and 6 months, respectively. Weekly backup tapes are stored offsite. The AHC-IS servers provide a stable, secure, well-maintained, and high-capacity data storage environment, and both REDCap and MySQL are widely-used, powerful, reliable, well-supported systems. Access to the study's data in REDCap will be restricted to the members of the study team by username and password. If participants are unable to complete a visit at the research site or complete a home visit, study staff members may send a hyperlink to participants to complete REDCap questionnaires remotely online.

If participants are unable to complete a visit at the research site or complete a home visit, study staff members may also use Zoom Video Conferencing to video chat with participants and complete interviews, questionnaires, and research tasks. Zoom is a communications software that allows video conferencing, online meetings, chat, and mobile collaboration. Zoom is HIPAA (signed BAA) and PIPEDA/PHIPA compliant with complete end-to-end 256-bit AES encryption. Zoom does not have access to identifiable health information and encrypts all audio and video data. The study team will not record audio or video through Zoom software; instead, recordings will be captured on a secure independent

device (i.e., audio recorder), uploaded to Box Secure Storage, and promptly deleted off the device to maintain HIPAA compliance. The exceptions are during the Baseline assessment, week 4, week 8, and week 16 appointments, which requires recording the 15 minute Conflict Negotiation Task. The recording will be done via Zoom software, uploaded to Box Secure Storage, and promptly deleted off the device to maintain HIPAA compliance.

Therapists will record their weekly sessions with participants to 1) ensure reliability for therapists assigned to the IPT-A condition and 2) identify characteristics of therapeutic orientation for therapists assigned to the usual care condition. Therapists will record their sessions using a digital audio recorder. Therapists will upload these audio recordings onto secure work computers at PrairieCare or Minnesota Mental Health Clinics and then transfer recordings into cloud-based storage platform Box Secure Storage. Box offers HIPAA and HITECH-compliant storage for all its users, and holds a signed HIPAA Business Associate Agreement (BAA) with the University of Minnesota. The storage platform demonstrates compliance through encrypting all uploaded data, both in transit and in storage, restricting physical access to production servers, and providing strict administrative controls which customers to configure user authorization to edit, download, password-protect, etc. An evaluation report (HIPAA AUP) issued by an independent third-party auditor detailing Box's HIPAA compliance is available upon request to Box customer services. Upon uploading audio files to Box, therapists will delete the audio file from their secure computer and from the recording device. The research team may then access the files for review through Box Secure Storage through secure UMN servers.

In circumstances when it is not feasible for the therapist to use a digital audio recorder (e.g. the therapists is conducting the therapy session via telehealth and needs to wear headphones), the therapist will use Zoom to record the therapy sessions. Zoom saves the video and audio data in separate files on the therapist's secure work computer. Therapists will upload only the audio file to Box. Upon uploading the audio file to Box, therapists will delete both the audio and video files from their secure computer.

Other study databases will be password protected and the database password will be changed on a regular basis. The UMN computing systems are 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 UMN. During data analysis, all identifying information, with the exception of the subject ID is removed from the data. No information about identities of the study participants will be published or presented at conferences.

Procedures for minimizing risks of audiotaping/videotaping. Digital audio files of treatment and assessment sessions, and digital video files of the parent-adolescent communication task will be coded by subject identification number, date, and the study name. Recorders will be kept in a locked box in the Research Coordinator's office until transferred to an electronic file. Digital recordings will be transferred to an electronic, password protected file within three days. Once the recording is transferred to an electronic file, it will be deleted from the recorder or computer. These files will all be accessible to only a limited number of project personnel. The University of Minnesota's computing system is protected from outside access. Only study IDs will be used to link audio/video files to questionnaire data.

Disclosure of health risk behaviors by the adolescent. 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.

Reporting of child abuse. Because information relating to abuse will be assessed (an item in the PTSD section of the K-SADS-PL),[118], 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.

Reproduction Risks: The impact of SSRIs on fetuses is currently unclear. Prior to initiation of the SSRI, all female patients will be asked by the psychpharmacologist, "Is it possible that you could be pregnant?" and "Have you recently or are you currently having any unprotected sex?" If a female patient endorses either of these questions, they will be counseled on the risks of taking an SSRI and encouraged to practice safe sex practices. If the patient believes she may be pregnant, she will be instructed to take a pregnancy test before beginning medication. If a patient is pregnant, medication management will not be initiated. If a female adolescent who is taking an SSRI becomes pregnant over the course of the trial, her psychopharmacologist will provide council on the potential risks and benefits of continuing the medication. If the patient and psychopharmacologist decide to discontinue the medication, the patient can continue to receive IPT-A and continue to participate in the study assessments.

Risks to Others: N/A

## 15.0 Potential Benefits to Participants

Potential Benefits: The benefit of participation in this study is receiving an active treatment (IPT-A with or without an SSRI or UC). IPT-A is an evidence-based

treatment that is not currently available in most community settings. The participants that are randomized to the treatment condition that includes IPT-A will be getting access to an evidence-based treatment that is not currently available at PrairieCare or Minnesota Mental Health Clinics.

## 16.0 Data Management

Data Analysis Plan: The proposed trial design of adaptive interventions is similar to a factorial design.[31,136-138] All analyses will be by intention-to-treat.

Aim 1. Hypotheses 1a and 1b: We will compare the average 16-week change in depressive symptoms (CDRS-R) and interpersonal functioning between adolescents compliant with ATS1 (cells 1 and 3) and UC (cell 4) and between adolescents compliant with ATS2 (cells 1 and 2) and UC (cell 4) using weighted t-tests. Secondary analyses will compare these groups using weighted regression adjusting for baseline characteristics such as age, gender, and depression severity. The measure of interpersonal functioning will be constructed from a latent factor analysis of changes in IPPA, IC, and parent-adolescent conflict behaviors. Note that the (unweighted) sample mean of adolescents in cells 1 and 2 contains an underrepresentation from adolescents with an insufficient response (compared to the population in which all adolescents followed ATS1) because half of the insufficient responders are re-randomized into subgroup 2 whereas the responding adolescents are not re-randomized. We can correct for this underrepresentation by weighting insufficient responders by 2.[139-141]

Hypothesis 1c: Incremental cost-effectiveness ratios between the two contrast pairs (ATS1 vs. UC and ATS2 vs. UC) will be calculated from the weighted mean scores for the change in costs and QALYs, and adjusted mean scores, based on weighted regression analysis (weights described above). Probabilistic sensitivity analysis will be conducted to account for uncertainty in the parameters. Bootstrapping with replacement will be used to construct cost-effectiveness scatter plots and cost-effectiveness acceptability curves. Following the 2nd Panel guidelines,[142] the analysis will be conducted from both a healthcare sector and societal perspective, and an Impact Inventory will be provided.

Aim 2: We will fit a linear regression model for change in depressive symptoms including a term for 4-week change in interpersonal functioning, first-stage treatment, and other confounders of the mediator-outcome relationship and a model for change in relationship functioning with first-stage treatment and other covariates as predictors. The controlled direct effect can be estimated using the regression coefficient for first-line treatment in the adjusted outcome model and the indirect effect can be estimated as the product of the coefficient for first-line treatment in the outcome and mediator models.

Aim 3: We will first test the effect of baseline relationship functioning as a moderator of stage 1 treatment (IPT-A vs. UC) by fitting a regression model for 16-week change in depression symptoms with baseline relationship functioning and an interaction between stage 1 treatment and baseline relationship functioning as covariates. Similarly, to assess the effect of 4-week change in relationship functioning and other possible covariates listed in the assessment section as moderators of second-stage treatment assignment, we will fit a regression model for change in depressive symptoms among insufficient responders among those initially randomized to IPT-A and include a term for 4-week change in relationship functioning and other covariates, second stage treatment (increased IPT-A vs. SSRI), and their interaction.

Secondary Analyses: In addition to modeling the change in depressive symptoms at 16 weeks, we will also use linear mixed-effect models (growth curve models) to model the depressive symptoms over time (up to 36 weeks) within each of the 2 embedded ATSs. Importantly, the data collected as part of this trial will also permit us to explore how to tailor the interventions based on an individual's characteristics, such as age, depression severity, or interpersonal functioning through the use of Q- and A-learning.[143,144,145,146,147,148,149,150,151,152,153]

Aim 4**:** Descriptive results regarding subject consent and the demographics for those who consented and declined will be reported as percentages. Chi-square tests will compare the proportion of subjects consented based on diagnostic and demographic characteristics. Adolescents', parents', and therapists' attitudes regarding the ATSs will be reported as mean scores and standard deviations on the CSQ-8 and ATA. Clinic staff members' attitudes regarding the evidence for the ATSs and the clinics' organizational readiness will be reported as mean scores and standard deviations on the ORCA Evidence and Context scales. Research team members will independently read transcripts of the treatment provider and leadership interviews and Research Team Observational Log, meet to discuss observed themes, and code the transcripts and logs.[154] Structural coding will assign similar responses to a broad common code. Initial development of the coding list will focus on particular domains of interest, such as attitudes towards the ATSs, barriers to implementation, facilitators of implementation, and recommendations for improvement. As new ideas are identified in subsequent transcripts, new codes will be assigned. When coding is completed, the code list will be collapsed into categories that will yield descriptive overarching themes. Coding will be conducted using Atlas.ti qualitative software.

Genetic and epigenetic association testing with treatment response phenotypes: We will use the Illumina PsychChip which contains the relevant candidate genes for study. Dr. Bishop has experience with this array[155,156] and will use standard genotyping and QC procedures prior to analysis. Genes selected for candidate gene studies are based on a range of -omic studies. Therefore, we will conduct set-based analyses using PLINK[157] or Golden Helix SNP Variation Suite software

(GoldenHelix SVS) to generate permutation-adjusted gene-based p-values from models containing relevant covariates. In order to assess methylation across the entire genome, this study will use the Infinium MethylationEPIC Array which quantitatively measures DNA methylation at 850K sites across the genome. Samples from subjects receiving the different treatments will be evenly distributed across the arrays to minimize batch effects. Two non-study controls will be placed on each array for QA/WC. The variables of interest are % methylation calculated from the ratio of a methylated probe relative to the sum of methylated and unmethylated probes ranging from 0 (unmethylated) to 1 (fully methylated). After obtaining % DNA methylation data, we will filter out low quality samples and probes based on call rates and QC parameters provided by the manufacturer. Additionally, as we have done in previous studies, we will remove probes that may cross-hybridize to multiple genomic regions, as well as probes that contain common SNPs (MAF≥0.01).[158] We will remove any experimental batch effects using a standard approach.[159] Cell-composition effects will be controlled for using established bioinformatic methods.[160] Association studies will examine mean methylation across specific regulatory regions for each candidate gene covered by the array in relation to treatment response status.

Analyses of SNP and methylation predictors define response categorically according to the HRSD assessment at week 4 (non-responders show < 20% improvement) or week 8 (non-responders show <40% improvement). Genetically defined race (PCA), sex, and age will be included in all models as we have done previously.[158,161] Covariates to be included in analysis include current medications which may influence methylation, particularly mood stabilizers,[162] sex, and smoking status.[163] Univariate assessments of intervention type (ATS1, ATS2, and UC), evidence of early trauma, lifetime trauma load, depressive symptoms, substance use exposures, medication utilization (antidepressants, anticonvulsants, antipsychotics, etc) will be examined to determine whether these variables require inclusion into our statistical models. Based on logistic regression models identifying significant predictors of clinical improvement, we may also create propensity scores which will be used as covariates in the analyses. We will compare % methylation at the pre-treatment time point in those who went on to respond versus those who did not, using analysis of covariance. Secondary analyses will examine HRSD and CDRS-R scores over multiple time points using mixed regression models (growth curve models) to examine the effect of % baseline methylation on symptom levels over time (baseline, wk4, wk8, wk16, wk32). Intercept and slopes will be fitted as random terms in the models of intraindividual change. We will be testing for a significant interaction between % baseline methylation and symptom change over time. We will use mixed regression models to examine the relationship between changes in HRSD and CDRS-R scores with % methylation changes longitudinally to identify whether change in methylation is correlated with HRSD and CDRS-R change scores. We will examine methylation changes from baseline to 8wks and 16wks in relation to responder status. We will first identify methylation changes that occur in

responders but not non-responders. Finally we will model % baseline methylation as a continuous outcome in relation to HRSD and CDRS-R scores across multiple time points. We will apply an unsupervised clustering approach to identify self-organizing maps[164] defining clusters of individuals with similar trajectories over time. Using the identified clusters, we will test for markers with baseline methylation level specific to these groups. Genes associated with response will be evaluated for pathway enrichment via Gene Ontology, as well as representation in biological network clusters with Ingenuity Pathway Analysis IPA® (QIAGEN Redwood City, www.qiagen.com/ingenuity) for enrichment of regulatory pathways. For HPA-axis, inflammation, and neuroendocrine pathways implicated a priori, we will test specifically for over enrichment in those pathways using a hypergeometric distribution test.

Power Analysis: The proposed trial is powered for a comparison of average change in depressive symptoms (Hypothesis 1a) and interpersonal functioning (Hypothesis 1b) between ATS1 & UC and ATS2 & UC. The power calculation for Hypotheses 1a and 1b is similar to a standard two-arm intervention trial with subject or case weights due to over- or under-sampling certain subgroups.[165,166] Table 2 gives the power for Hypotheses 1a and 1b assuming a total sample size of 200 and 2:1 allocation under different assumptions of the effect size (ES) (Cohen's d) between the ATSs beginning with IPT-A and UC. We consider an ES of 0.50 to be of interest; previous studies of IPT-A alone versus non-adaptive treatment as usual demonstrated similar ESs and we believe that similar ESs will be obtained comparing the ATSs with UC (which may be adaptive).[17] Pilot data of these ATSs have demonstrated that approximately 50% of subjects will be responders and we demonstrate that adequate power is achieved across a range of plausible proportion of responders to IPT-A.

Although the trial was powered to test the hypotheses for the primary aim, we demonstrate that we have adequate power to test for mediators (Hypothesis 2) and moderators of the first-line treatment effect (Hypothesis 3a) under plausible scenarios. Dietz et al. found that approximately 55% of the effect of family-based IPT-A on depressive symptoms was mediated by changes in interpersonal functioning.[167] If we assume that 4 week changes in interpersonal functioning mediates between 30-50% of the total effect, we will have between 78% and 99.5% power to detect a significant indirect effect. For ease of power estimates, we dichotomized the moderator (e.g. interpersonal functioning) into two groups with ~50% of the population in each group. If the overall effect size between those randomized initially to IPT-A versus UC is between 0.45 and 0.5 and the effect size among those with high baseline relationship functioning is between 0.0 - 0.1,[168] we will have 75%-95% power to detect a significant interaction effect between first-line treatment and interpersonal functioning assuming a two-sided Wald-type test using a 90% significance level. Treating interpersonal functioning as a continuous covariate would increase the power to detect a significant interaction.

Table 2. Power to test a difference in the average 16-week change (e.g., depressive symptoms, interpersonal functioning) between one of the IPT-A ATSs and UC. Power calculations assume total N=200, a 2:1 allocation ratio, and the use of a two-sided weighted t-test with a 95% significance level.

| | Effect Size | | |
|---|---|---|---|
| Proportion of Responders | 0.45 | 0.50 | 0.55 |
| 0.3 | 77% | 85% | 91% |
| 0.5 | 79% | 87% | 92% |
| 0.7 | 82% | 88% | 94% |

Data Integrity: Participant self-report, parent-report, and clinician report measures will immediately checked upon completion by a research assistant to identify unintentionally missing data. Paper measures will be entered into a de-identified electron*ic database, and entry will be double checked for accuracy by a second research assistant. Scoring will also be double checked for accuracy by a second research assistant.*

## 17.0 Confidentiality

Data Security: The PI will emphasize the critical importance of subject confidentiality in the training of all project staff, and will reiterate this point as opportunities arise in handling of such material. All interviews and therapy sessions will take place in private rooms. All off-site communication between research staff and participants will occur by telephone or by email using the University's email encryption system to ensure security. If text messaging or unencrypted email is used to communicate between research staff and participants, it will only be used after participants provide consent and complete the appropriate authorization forms. In order to safeguard the confidentiality and security of data files, participants (adolescents and parents) 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 subject ID numbers will be the only unique piece of information linking the data files to the consent file. 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.

Data for this study will be entered into a REDCap database, which uses a MySQL database via a secure web interface with data checks used during data entry to

ensure data quality. REDCap includes a complete suite of features to support HIPAA compliance, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. The MySQL database and the web server will both be housed on secure servers operated by the University of Minnesota Academic Health Center's Information Systems group (AHC-IS). The servers are in a physically secure location on campus and are backed up nightly, with the backups stored in accordance with the AHC-IS retention schedule of daily, weekly, and monthly tapes retained for 1 month, 3 months, and 6 months, respectively. Weekly backup tapes are stored offsite. The AHC-IS servers provide a stable, secure, well-maintained, and high-capacity data storage environment, and both REDCap and MySQL are widely-used, powerful, reliable, well-supported systems. Access to the study's data in REDCap will be restricted to the members of the study team by username and password.

Therapists will record their weekly sessions with participants to 1) ensure reliability for therapists assigned to the IPT-A condition and 2) identify characteristics of therapeutic orientation for therapists assigned to the usual care condition. Therapists will record their sessions using a digital audio recorder. Therapists will upload these audio recordings onto secure work computers at PrairieCare or Minnesota Mental Health Clinics and then transfer recordings into cloud-based storage platform Box Secure Storage. Box offers HIPAA and HITECH-compliant storage for all its users, and holds a signed HIPAA Business Associate Agreement (BAA) with the University of Minnesota. The storage platform demonstrates compliance through encrypting all uploaded data, both in transit and in storage, restricting physical access to production servers, and providing strict administrative controls which customers to configure user authorization to edit, download, password-protect, etc. An evaluation report (HIPAA AUP) issued by an independent third-party auditor detailing Box's HIPAA compliance is available upon request to Box customer services. Upon uploading audio files to Box, therapists will delete the audio file, and any video files, from their secure computer and from the recording device. The research team may then access the files for review through Box Secure Storage through secure UMN servers.

In circumstances when it is not feasible for the therapist to use a digital audio recorder (e.g. the therapists is conducting the therapy session via telehealth and needs to wear headphones), the therapist will use Zoom to record the therapy sessions. Zoom saves the video and audio data in separate files on the therapist's secure work computer. Therapists will upload only the audio file to Box. Upon uploading the audio file to Box, therapists will delete both the audio and video files from their secure computer.

Other study databases will be password protected and the database password will be changed on a regular basis. The UMN computing systems are 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 UMN. During data analysis, all identifying information, with the exception of the subject ID is removed from the data. No information about identities of the study participants will be published or presented at conferences.

Procedures for minimizing risks of audiotaping/videotaping. See Section 14.

Disclosure of health risk behaviors by the adolescent. See Section 14.

Reporting of child abuse. See Section 14.

No research study information, including copies of consent forms, will be placed in the participants' medical, employment, or educational records.

## 18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

Data Integrity Monitoring. Research team members will meet regularly to discuss study progress, ensure data integrity, and that the study is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, and applicable regulatory requirements. Study team members will be instructed to bring any identified protocol violations to the PI in a timely fashion and team members will be re-trained, if needed.

Data Safety Monitoring. The PI's monitoring of data will be ongoing throughout the project. Information regarding symptom severity, adverse events, and suicidality will be collected by IEs during the assessments. Any adverse events or suicidality that is reported to therapists during psychotherapy or psychopharmacology sessions will also be recorded, and treatment providers 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. Therapists will report on the progress of their cases during weekly supervision with the PI. The PI will monitor all data and will be available to study staff.

Data and Safety Monitoring Board. The PI will convene a Data and Safety Monitoring Board (DSMB). The DSMB will include a biostatistician with expertise in randomized clinical trial methodology, a researcher with expertise in adolescent depression, and a clinical psychologist or psychiatrist. The members of the DSMB will not be involved in this project and will not be collaborators on any other of the investigators' projects nor in their employ. DSMB members will provide the NIMH with qualifications and a COI statement indicating that they have no direct involvement with the study or COI with the investigators or institutions conducting the study. They will meet annually to 1) monitor the safety, quality and conduct of this study and 2) decide whether adequate subject

safeguards are in place. The DSMB 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. The biostatistician will be responsible for generating a deidentified annual report of key events that will be reviewed as part of the safety monitoring of the protocol. The tentative list of key events will include serious adverse events and more specifically: 1) suicide behaviors, 2) hospitalization, 3) school drop-out, 4) arrests, 5) pregnancies, 6) premature drop-out from treatment, 7) depression symptoms, and 8) medication adherence and medication side effects. The key events will be reviewed at the first meeting of the DSMB to obtain the 3 DSMB members' input into the list and to add any other events or measures that they feel would be relevant to include for evaluating the safety and conduct of the clinical trial.

Reporting. All investigators will report unexpected serious adverse events (SAEs) or unanticipated problems involving risks to subjects to the IRB and to the assigned NIMH PO. Reports will be made to the (DSMB, as detailed above. If DSMB notes serious and unexpected adverse events, or unanticipated problems involving risks to subjects or others which are related to the study, the PI and IRB will be notified. This will be done via a letter from the DSMB Chair/Administrator to the PI for distribution to the institutional official, sponsor, and IRB. 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 PI will report to the IRB and the assigned NIMH PO within the following timeframe: (1) IRB/ISM/DSMB suspensions or terminations (within 3 business days), (2) deaths related to study participation (within 5 business days), (3) unexpected serious adverse events (within 10 business days), (4) unanticipated problems involving risks to subjects or others (within 10 business days), (5) serious or continuing noncompliance (within 10 business days), (6) adverse events deemed expected or unrelated to the study (with annual progress report), and (7) protocol violations (with annual progress report).

# 19.0 Provisions to Protect the Privacy Interests of Participants

Protecting Privacy: All consent procedures, assessments, and study activities will be conducted in private rooms by trained personnel. Dr. Gunlicks-Stoessel, a child psychologist, or trained psychology practicum students will administer all psychiatric diagnostic interviews and measures. Participants will be repeatedly reminded that sharing of information and completion of study tasks are voluntary. Assessment of participant comfort will occur on an ongoing basis; research staff will ask the youth how they are feeling and if they are comfortable with starting/continuing a study activity. Parents and children will be given the opportunity to separately discuss concerns or responses to questions with research staff. Since we are working with minors, we will inform participants and their parent(s) that we are required to report if the subject is a danger to themselves or others or if they report child abuse/neglect.

Access to Participants: Accessing the participant's medical record to obtain information regarding treatment history will be described in the consent form signed by the participant. Participants will be informed that they may withdraw this consent at any time.

## 20.0 Compensation for Research-Related Injury

Compensation for Research-Related Injury: The following statement is included in the consent form: "In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. If you think that you have suffered a research related injury let the study physicians know right away."

Contract Language: N/A

## 21.0 Consent Process

Consent Process (when consent will be obtained) for Adolescents and Parents: Potential participants who learn about the study from PrairieCare or Minnesota Mental Health Clinic staff will call University of Minnesota research staff to express interest in participating in the study. Research staff will also directly contact potential participants if they have signed a Permission to Contact form. The researchers will schedule an appointment for the consent process to occur.

<u>For participants recruited via PrairieCare, Minnesota Mental Health Clinics, or referred from partnering organizations who opt to schedule a screening appointment:</u> Families will schedule a brief screening assessment to confirm eligibility. Prior to completing this screening, parents and adolescents will complete "consent/assent to screen" forms indicating their willingness to participate in the screening process. Upon the completion of the screening process, eligible participants interested in the study will schedule a subsequent baseline assessment; at the baseline appointment, the study team will conduct informed consent for participation in the study.

For participants self-referred or participants referred that opt out of the scheduled screening option: Families will complete a "consent to contact form" which will be faxed to the research team, indicating parents' permission to be contacted by research staff. Potential participants may also call University of Minnesota research staff to express interest in participating in the study. Parents will participate in a structured telephone screen with study staff that asks about mood, medical history, and current and prior treatment. If the adolescent appears eligible on the phone screen, they will be asked to meet with an independent evaluator (IE) to learn more about the study, provide consent/assent, and complete the baseline assessments to determine eligibility.

Only members of the University of Minnesota research team will conduct the informed consent. During the consent meeting, the study will be explained; the consent forms will be reviewed in detail; any questions will be answered; and ability to understand will be assessed. Research staff will reiterate that the participants' agreeing or declining to participate will have no bearing on their care at their chosen mental health clinic. Consent and assent forms will be signed if the parent and adolescent choose to participate. For participants who are not able to come to the University of Minnesota or are unable to do a home visit, the consent procedure will be conducted via a secure web-conferencing platform (Zoom). A member of the research team will review the consent form over Zoom and a copy will be available to participant via REDCap to electronically sign.

Consent Process for Therapists and Other Clinic Staff: Clinic staff at PrairieCare or Minnesota Mental Health Clinics will be informed about participation in the study by members of the clinic's leadership team. Clinic staff who are interested in participating will contact University of Minnesota research staff to indicate interest in participating in the study. Only members of the University of Minnesota research team will conduct the informed consent. During the consent meeting, the study will be explained; the consent forms will be reviewed in detail; any questions will be answered; and ability to understand will be assessed. Research staff will reiterate that the participants' agreeing or declining to participate will have no bearing on their employment at their clinic. Consent forms will be signed if the individual chooses to participate.

Waiver or Alteration of Consent Process (when consent will not be obtained):

N/A

Non-English Speaking Participants:

N/A

Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age):

For adolescents younger than 18 years of age, the permission to contact form must be signed by their parent or legal guardian. Subsequent contact with these youth and their parent or guardian will include both consent and assent processes. Only one parent will be required to give consent. Research staff may accept signed consent from legal guardians if they provide documentation of their authority to consent to the youth's general medical care. Assent will be required for all adolescents younger than 18 years of age. Youth assent will be documented by their signature on the Youth Assent Form.

Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent:

- For adolescents 18 years of age, research staff conducting the consent meeting will administer the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) to assess capacity to consent.
- During study visits, the independent evaluators conduct semi-structured interview assessments of depression symptoms and psychosocial functioning. If during these assessments, they observe responses or behavior that suggest impaired competence, they will ensure that a qualified staff administer the MacCAT-CR to determine if capacity to consent has changed and requires permission from the legally authorized representative in order to continue participation in the study. The legally authorized representative will be notified and permission will be sought with the main study consent form if the LAR has not already provided consent. The LAR will be involved in the entire consent process each time capacity to consent is re-evaluated.
- Participants that are 18 years old or older during study participation will be asked to document their wishes regarding future study participation in the event that their capacity to consent fluctuates. Documentation will be part of the participant's consent records for reference, but the legally authorized representative's permission is still required in the event that the participant does not have capacity to consent.
- To avoid seeking consent during periods of greater than normal impairment, we are not enrolling participants during hospitalizations. We are also not enrolling adolescents who are actively suicidal with a plan and/or intent who are assessed to need a higher level of care than outpatient treatment. Once stabilized, the adolescent can be re-evaluated for eligibility to participate in the study.

Adults Unable to Consent:

- For adolescents 18 years of age or older with diminished/fluctuating capacity to consent, we will ask this participant to sign the assent form and their LAR to sign the main consent form.

## 22.0 Setting

Research Sites: The treatment delivered in this study will be provided at PrairieCare and Minnesota Mental Health Clinics by treatment providers already employed by the clinics. The research assessments will be administered either at the mental health clinic or at the University of Minnesota. If a family is unable to complete an assessment at the community mental health clinic or at the University of Minnesota, research staff will travel to the family's home and conduct the research assessment there (in this case, EEG data will not be collected). For the week 4, week 8, week 12, week 16, and week 36 assessments, if the family is not able to complete the assessment at the community mental health clinic or at the University of Minnesota, and the family is also not able to do a home visit, research staff will attempt to collect interview and questionnaire measures by 1) telephone, 2) Zoom Video Conferencing, and/or 3) hyperlinks to online REDCap questionnaires.

## 23.0 Multi-Site Research

N/A

## 24.0 Resources Available

Resources Available:

Feasibility of Recruitment: PrairieCare completes over 4,000 psychiatric needs assessments per year and provides treatment to approximately 1000 depressed adolescents annually. Last year, over 300 adolescents with a diagnosis of depression initiated psychotherapy services in the outpatient clinics. This will be sufficient to recruit and enroll 200 participants over the course of 4 years. Minnesota Mental Health Clinics provided services to over 700 adolescents with a diagnosis of depression in the past year.

The proposed time period for this research is 5 years.

Facilities:

Research Office Space: The investigators have adequate faculty office space and resources in their respective departments (Psychiatry, Biostatistics, and Health Policy & Management) to conduct the proposed research activities. Office space

in the University's Institute for Translational Research in Children's Mental Health (ITR) will be utilized to house the Project Director, Research Coordinator, and Evaluators. Space in ITR will also secure (per HIPAA and IRB standards) all incoming and processing of data. In addition to daily research activities, training and staff meetings will be held at this location. This space will be capable of maintaining the required number of staff, technological, storage and training amenities to maximally perform the duties outlined in this grant.

Research Laboratory Space: All biological specimens (saliva, DNA and RNA) collected through this protocol will be stored in the laboratory of Dr. Jeffrey R. Bishop at the University of Minnesota (516 Delaware Street S.E. Phillips-Wangensteen Building room B150 Minneapolis, MN 55455). Dr. Bishop's laboratory is within the College of Pharmacy's Department of Experimental and Clinical Pharmacology Pharmacogenomics Laboratory located at B-150 Phillips-Wangensteen Building. It contains office space for twelve additional researchers (students/fellows/staff). It is comprised of over 3,000 square feet of main laboratory space, plus auxiliary lab rooms and conference space. The pharmacogenomics laboratory is designed for targeted genotyping and functional characterization studies. This new, state of art laboratory is functionally divided into several work areas including those for molecular genetics, biochemical analysis, cell culture and analytical analysis. There is a dedicated biological safety cabinet for human biospecimen processing. The laboratory specializes in the isolation of nucleic acids (DNA, RNA, protein) from various biospecimen types such as serum, plasma, whole blood, isolated PBMCs, fresh/frozen/paraffin embedded (FFPE) tissue, saliva, and buccal swabs using validated and standardized protocols, and is capable of high capacity biospecimen storage. The laboratory also houses a 365 square-foot in-vitro cell culture room containing four biological safety cabinets, two stacked incubators, and one HERAcell 150i CO2 incubator for functional characterization studies utilizing multiple cell modeling techniques.
Computers: All investigators and research staff have adequate computer and software resources to meet the demands of the study. The investigative team benefits from several computer and server resources provided by the University of Minnesota, including a sophisticated data protection and back-up system.

Treatment Sites: Treatment providers will deliver services at PrairieCare or Minnesota Mental Health Clinics outpatient clinic sites. They have adequate space to carry out participant programming activities, as well as record, store and maintain confidential client files per HIPAA and IRB protocols.

Medical or psychological resources that participants might need as a result of any anticipated or unanticipated consequences of the research are available at PrairieCare, Minnesota Mental Health Clinics, and University of Minnesota Medical Center.

Research staff and mental health clinic staff who are involved in recruiting and treating participants will be trained in the protocol, procedures, and their respective duties and functions by the PI or Co-Investigators. If any future revisions are made to the protocol or study procedures, research staff and mental health clinic staff will be promptly trained in the revised procedures. Research staff and their training dates will be documented on the Delegation Log in the study regulatory binder.

## 25.0 References

**References**

1. Costello EJ, Erkanli A, Angold A. Is there an epidemic of child or adolescent depression? *Journal of Child Psychology and Psychiatry.* 2006;47:1263-1271.
2. Lewinsohn PM, Hops H, Roberts RE, Seeley JR, Andrews JA. Adolescent psychopathology: I. Prevalence and incidence of depression and other DSM-III-R disorders in high school students. *Journal of Abnormal Psychology.* 1993;102:133-144.
3. Glied S, Pine DS. Consequences and correlates of adolescent depression. *Archives of Pediatric Adolescent Medicine.* 2002;156:1009-1014.
4. Lewinsohn PM, Roberts RE, Seeley JR, Rohde P, Gotlib IH, Hops H. Adolescent psychopathology II: Psychosocial risk factors for depression. *Journal of Abnormal Psychology.* 1994;103:302-315.
5. Shaffer D, Pfeffer CR, Bernet W, Arnold V, Beitchman J, Benson RS. Practice parameter for the assessment and treatment of children and adolescents with suicidal behavior. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2001;40(Suppl. 7):24S-51S.
6. Foster EM, Heier-Leitzell B, the Conduct Problems Prevention Research Group. The public costs of depression in adolescent girls. In: Strauman TJ, Costanzo PR, Garber J, eds. *Depression in Adolescent Girls: Science and Prevention.* New York: Guilford Press; 2011:97-111.
7. Lynch FL, Clark GN. Estimating the economic burden of depression in children and adolescents. *American Journal of Preventive Medicine.* 2006;31:143-151.
8. Lewinsohn PM, Rohde P, Klein DN, Seeley JR. Natural course of adolescent major depressive disorder: I. Continuity into young adulthood. *Journal of the American Academy of Child and Adolescent Psychiatry.* 1999;38:56-63.
9. Weissman MM, Wolk S, Goldstein RB, et al. Depressed adolescents grown up. *Journal of the American Medical Association.* 1999;281:1707-1713.
10. Birmaher B, Brent D. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2007;46:1503-1526.

11. David-Ferdon C, Kaslow NJ. Evidence-based psychosocial treatments for child and adolescent depression. *Journal of Clinical Child and Adolescent Psychology.* 2008;37:62-104.
12. Emslie GJ, Heiligenstein JH, Wagner KD, et al. Fluoxetine for active treatment of depression in children and adolescents: A placebo-controlled, randomized clinical trial. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2002;41:1205-1215.
13. Keller MB, Ryan ND, Strober M, et al. Efficacy of paroxetine in the treatment of adolescent major depression: A randomized, controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2001;40:762-772.
14. Kennard B, Silva S, Vitiello B, et al. Remission and residual symptoms after short-term treatment in the Treatment of Adolescents with Depression Study (TADS). *Journal of the American Academy of Child and Adolescent Psychiatry.* 2006;45:1404-1411.
15. Wagner KD, Ambrosini P, Rynn M, et al. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: Two randomized controlled trials. *Journal of the American Medical Association.* 2003;290:1033-1041.
16. Wagner KD, Jonas J, Findling RL, Ventura D, Saikali K. A double-blind, randomized, placebo-controlled trial of escitalopram in the treatment of pediatric depression. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2006;45:280-288.
17. Mufson L, Dorta KP, Wickramaratne P, Nomura Y, Olfson M, Weissman MM. A randomized effectiveness trial of interpersonal psychotherapy for depressed adolescents. *Archives of General Psychiatry.* 2004;61:577-584.
18. TADS Team. Fluoxetine, cognitive–behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents with Depression Study (TADS) randomized controlled trial. *Journal of the American Medical Association.* 2004;292:807-820.
19. Lewandowski RE, Acri MC, Hoagwood KE, et al. Evidence for the management of adolescent depression. *Pediatrics.* 2013;132:e996-e1009.
20. Harmon C, Lambert MJ, Smart DW, et al. Enhancing outcome for potential treatment failures: Therapist/client feedback and clinical support tools. *Psychotherapy Research.* 2007;17:379-392.
21. Hawkins EJ, Lambert MJ, Vermeersch DA, Slade K, Tuttle K. The effects of providing patient progress information to therapists and patients. *Psychotherapy Research.* 2004;14:308-327.
22. Lambert MJ, Harmon C, Slade K, Whipple JL, Hawkins EJ. Providing feedback to psychotherapists on their patients' progress: Clinical results and practice suggestions. *Journal of Clinical Psychology.* 2005;61:165-174.
23. Lambert MJ, Shimokawa K. Collecting client feedback. *Psychotherapy* 2011;48:72-79.
24. Lambert MJ, Whipple JL, Smart DW, Vermeersch DA, Nielsen SL, Hawkins EJ. The effects of providing therapists with feedback on patient progress during

psychotherapy: Are outcomes enhanced? *Psychotherapy Research.* 2001;11:49-68.
25. Lambert MJ, Whipple JL, Vermeersch DA, et al. Enhancing psychotherapy outcomes via providing feedback on patient progress: A replication. *Clinical Psychology and Psychotherapy.* 2002;9:91-103.
26. Whipple JL, Lambert MJ, Vermeersch DA, Smart DW, Nielsen SL, Hawkins EJ. Improving the effects of psychotherapy: The use of early identification of treatment failure and problem solving strategies in routine practice. *Journal of Counseling Psychology.* 2003;58:59-68.
27. Lambert MJ. Presidential address: What we have learned from a decade of research aimed at improving psychotherapy outcome in routine care. *Psychotherapy Research.* 2007;17:1-14.
28. O'Connor BC, Lewandowski RE, Rodriguez S, et al. Usual care for adolescent depression from symptom identification through treatment initiation. *JAMA Pediatrics.* 2016;170:373-380.
29. Lavori PW, Dawson R. A design for testing clinical strategies: Biased individually tailored within-subject randomization. *Journal of the Royal Statistics Society.* 2000;163:29-38.
30. Lavori PW, Dawson R. Dynamic treatment regimes: Practical design considerations. *Clinical Trials.* 2003;1:9-20.
31. Murphy SA. An experimental design for the development of adaptive treatment stratgies. *Statistics in Medicine.* 2005;24:1455-1481.
32. Sobell M, Sobell L. Stepped care as a heuristic approach to the treatment of alcohol problems. *Journal of Consulting and Clinical Psychology.* 2000;68(573-579).
33. Katon W, Von Korff M, Lin E, Simon G. Rethinking practitioner roles in chronic illness: The specialist, primary care physician, and the practice nurse. *General Hospital Psychiatry* 2001;23:138-144.
34. Katon W, von Korff M., Lin E., et al. Stepped collaborative care for primary care patients with persistent symptoms of depression: A randomized trial. *Archives of General Psychiatry.* 1999;56:1109-1115.
35. van't Veer-Tazelaar PJ, van Marwijk HJ, van Oppen P, et al. Stepped-care prevention of anxiety and depression in late life: A randomized controlled trial. *Archives of General Psychiatry.* 2009;66:297-304.
36. Richardson LP, Ludman E, McCauley E, et al. Collaborative care for adolescents with depression in primary care: A randomized clinical trial. *Journal Of The American Medical Association.* 2014;312:809-816.
37. Caporino NE, Karver MS. The acceptability of treatments for depression to a community sample of adolescent girls. *Journal of Adolescence.* 2012;35(1237-1245).
38. Gunlicks-Stoessel M, Mufson L, Westervelt A, Almirall D, Murphy S. A pilot SMART for developing an adaptive treatment strategy for adolescent depression. *Journal of Clinical Child and Adolescent Psychology.* 2016;45:480-494.

39. Jaycox LH, Asarnow JR, Sherbourne CD, Rea MM, LaBorde AP, Wells KB. Adolescent primary care patients' preferences for depression treatment. *Administration and Policy in Mental Health and Mental Health Services Research.* 2006;33(2):198-207.
40. Mufson L, Dorta KP, Moreau D, Weissman MM. *Interpersonal psychotherapy for depressed adolescents.* 2 ed. New York: Guilford Press; 2004.
41. Hammen C. The emergence of an interpersonal approach to depression In: Joiner T, Coyne JC, eds. *The interactional nature of depression: Advances in interpersonal approaches.* Washington, DC: American Psychological Association; 1999:21-35.
42. Restifo K, Bögels S. Family processes in the development of youth depression: Translating the evidence to treatment. *Clinical Psychology Review.* 2009;29:294-316.
43. Rudolph KD, Hammen C, Burge D, Lindberg N, Herzberg D, Daley SE. Toward an interpersonal life-stress model of depression: The developmental context of stress generation. *Development and Psychopathology.* 2000;12:215-234.
44. Mufson L, Yanes-Lukin P, Anderson G. A pilot study of Brief IPT-A delivered in primary care. *General Hospital Psychiatry.* 2015;37:481-484.
45. Young JF, Benas JS, Schueler CM, Gallop R, Gillham JE, Mufson L. A randomized depression prevention trial comparing Interpersonal Psychotherapy--Adolescent Skills Training to group counseling in schools. *Prevention Science.* 2016;17:314-324.
46. Fixsen DL, Naoom SF, Blase KA, Friedman RM, Wallace F. Implementation research: A synthesis of the literature. In: Louis de la Parte Florida Mental Health Institute TNIRN, ed. Tampa, FL: University of South Florida2005.
47. Weisz JR, Southam-Gerow MA, Gordis EB, et al. Cognitive-behavioral therapy versus usual clinical care for youth depression: An initial test of transportability to community clinics and clinicians. *Journal of Consulting and Clinical Psychology.* 2009;77:383-396.
48. Weisz JR, Gordis EB, Chu BC, et al. Cognitive-behavioral therapy versus usual clinical care for yourth depression: An initial test of transportability to community clinics and clinicians. *Journal of Consulting and Clinical Psychology.* 2009;77(3):383-396.
49. Gunlicks-Stoessel ML, Mufson L. Early patterns of symptom change signal remission with interpersonal psychotherapy for depressed adolescents. *Depression & Anxiety.* 2011;28:525–531.
50. Williams JBW, Kobak KA, Bech P, et al. The GRID-HAMD: Standardization of the Hamilton Depression Rating Scale. *International Clinical Psychopharmacology.* 2008;23:120-129.
51. Brent D, Emslie G, Clarke G, et al. Switching to another SSRI or to venlafaxine with our without cognitive behavioral therapy for adolescents with SSRI-resistant depression. *Journal of the American Medical Association.* 2008;299:901-913.
52. Clarke GN, Debar L, Lynch F, et al. A randomized effectiveness trial of brief cognitive–behavioral therapy for depressed adolescents receiving antidepressant

medication *Journal of the American Academy of Child and Adolescent Psychiatry.* 2005;44:888-898.
53. Goodyer IM, Dubicka B, Wilkinson P, et al. Selective serotonin reuptake inhibitors (SSRIs) and routine specialist care with and without cognitive behaviour therapy in adolescents with major depression: Randomised controlled trial. *British Medical Journal* 2007.
54. Melvin GA, Tonge BJ, King NJ, Heyne D, Gordon MS, Klimkeit E. A comparison of cognitive-behavioral therapy, sertraline, and their combination for adolescent depression. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2006;45:1151-1161.
55. Clarke G, Rohde P, Lewinsohn P, Hops H, Seeley J. Cognitive-behavioral treatment of adolescent depression: Efficacy of acute group treatment and booster sessions. *Journal of the American Academy of Child & Adolescent Psychiatry.* 1999;38:272-279.
56. DeRubeis RJ, Hollon SD, Amsterdam JD, et al. Cognitive therapy vs medications in the treatment of moderate to severe depression. *Archives of General Psychiatry.* 2005;62:409-416.
57. Dimidjian S, Hollon SD, Dobson KS, et al. Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. *Journal of Consulting and Clinical Psychology.* 2006;74(4):658-670.
58. Lewinsohn PM, Clarke GN, Hops H, Andrews J. Cognitive-behavioral treatment of depressed adolescents. *Behavior Therapy.* 1990;21:385-401.
59. Mufson L, Weissman MM, Moreau D, Garfinkel R. Efficacy of interpersonal psychotherapy for depressed adolescents. *Archives of General Psychiatry.* 1999;56:573-579.
60. Kazdin AE. Mediators and mechanisms of change in psychotherapy research. *Annual Review of Clinical Psychology.* 2007;3:1-27.
61. Kazdin AE, Nock MK. Delineating mechanisms of change in child and adolescent therapy: Methodological issues and research recommendations. *Journal of Child Psychology & Psychiatry.* 2003;44:1116-1129.
62. Kwan BM, Dimidjian S, Rizvi SL. Treatment preference, engagement, and clinical improvement in pharmacotherapy versus psychotherapy for depression. *Behavior Research and Therapy.* 2010;48:799-804.
63. Spoth R, Redmond C. Research on family engagement in preventive interventions: Toward improved use of scientific findings in primary prevention practice. *Journal of Primary Prevention.* 2000;21:267-284.
64. Curry J, Rohde P, Simons A, et al. Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). *Journal of the American Academy of Child and Adolescent Psychiatry.* 2006;45:1427-1439.
65. Horowitz JL, Garber J, Ciesla JA, Young JF, Mufson L. Prevention of depressive symptoms in adolescents: A randomized trial of cognitive–behavioral and interpersonal prevention programs. *Journal of Consulting and Clinical Psychology.* 2007;75:693-706.

66. Young JF, Mufson L, Davies M. Impact of comorbid anxiety in an effectiveness study of interpersonal psychotherapy for depressed adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2006;45:904-912.
67. Kennard BD, Clarke GN, Weersing VR, et al. Effective components of TORDIA cognitive-behavioral therapy for adolescent depression: Preliminary findings. *Journal of Consulting and Clinical Psychology.* 2009;77:1033-1041.
68. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. *American Journal of Psychiatry.* 2000;157(10):1552-1562.
69. Baune BT, Hohoff C, Berger K, et al. Association of the COMT val158met variant with antidepressant treatment response in major depression. *Neuronpsychopharmacology.* 2008;33(924-32).
70. Fabbri C, Di Girolamo G, Serretti A. Pharmacogenetics of antidepressant drugs: an update after almost 20 years of research. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics.* 2013;162B:487-520.
71. Hortsmann S, Lucae S, Menke A, et al. Polymorphisms in GRIK4, HTR2A, and FKBP5 show interactive effects in predicting remission to antidepressant treatment. *Neuropsychopharmacology.* 2010;35:727-740.
72. Niitsu T, Fabbri C, Bentini F, Serretti A. Pharmacogenetics in major depression: a comprehensive meta-analysis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry.* 2013;45:183-194.
73. Winner J, Allen JD, Anthony AC, Spahic-Mihajlovic A. Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression. *Translational Psychiatry.* 2013;3:e242.
74. Domschke K, Dannlowski U, Ohrmann P, et al. Cannabinoid receptor 1 (CNR1) gene: impact on antidepressant treatment response and emotion processing in major depression. *European Neuropsychopharmacol.* 2008;18:751-759.
75. Baune BT, Hohoff C, Mortensen LS, Deckert J, Arolt V, Domscheke K. Serotonin transporter polymorphism (5-HTTLPR) association with melancholic depression: a female specific effect? . *Depression & Anxiety.* 2008;25:920-925.
76. Baffa A, Hohoff C, Baune BT, et al. Norepinephrine and serotonin transporter genes: impact on treatment response in depression. 2010;62:121-131.
77. Domschke K, Hohoff C, Mortensen LS, et al. Monoamine oxidase a variant influences antidepressant treatment response in female patients with major depression. *Biological Psychiatry.* 2008;32:224-228.
78. Baune BT, Dannlowski U, Domschke K, et al. The interleukin 1 beta (IL1B) gene is associated with failure to achieve remission and impaired emotion processing in major depression. *Biological Psychiatry.* 2010;67:543-549.
79. Kawaguchi DM, Glatt SJ. GRIK4 polymorphism and its association with antidepressant response in depressed patients: a meta-analysis. Pharmacogenomics. *Pharmacogenomics.* 2014;15:1451-1459.
80. Breitenstein B, Scheuer S, Pfister H, et al. The clinical application of ABCB1 genotyping in antidepressant treatment: a pilot study. *CNS Spectrums.* 2014;19:165-175.

81. Fabbri C, Serretti A. Pharmacogenetics of major depressive disorder: top genes and pathways toward clinical applications. *Current Psychiatry.* 2015.
82. Thakur M, Grossman I, McCrory DC, et al. Review of evidence for genetic testing for CYP450 polymorphisms in management of patients with nonpsychotic depression with selective serotonin reuptake inhibitors. *Genetics in Medicine.* 2007;9:826-835.
83. Hodgson K, Tansey K, Dernoysek MZ, et al. Genetic differences in cytochrome P450 enzymes and antidepressant treatment response. *Journal of Psychopharmacology.* 2014;28(2):133-141.
84. Garriock HA, Kraft JB, Shyn SI, et al. A genomewide association study of citalopram response in major depressive disorder. *Biological Psychiatry.* 2010;67:133-138.
85. Ising M, Lucae S, Binder EB, et al. A genomewide association study points to multiple loci that predict antidepressant drug treatment outcome in depression. *General Psychiatry.* 2009;66:966-975.
86. Biemacka JM, Sangkuhl K, Jenkins G, et al. The International SSRI Pharmacogenomics Consortium (ISPC): a genome-wide association study of antidepressant treatment response. *Translational Psychiatry.* 2015;5:e553.
87. Ji Y, Biemacka JM, Hebbring S, et al. Pharmacogenomics of selective serotonin reuptake inhibitor treatment for major depressive disorder: genome-wide associations and functional genomics. *The Pharmacogenomics Journal.* 2013;13:456-463.
88. Laje G, McMahon FJ. Genome-wide association studies of antidepressant outcome: A brief review. *Biological Psychiatry.* 2011;35:1553-1557.
89. Lisoway AJ, Zai CC, Tiwari AK, Kennedy JH. DNA methylation and clinical response to antidepressant medication in major depressive disorder: A review and recommendations. *Neuroscience Letters.* 2017.
90. Kanherkar RR, Bhatia-Dev N, Csoka AB. Epigenetics across the human lifespan. *Frontiers in Cell and Developmental Biology.* 2014;9(2).
91. Menke A, Klengel T, Binder EB. Epigenetics, depression and antidepressant treatment. *Current Pharmaceutical Design.* 2012;18(36):5879-5889.
92. Weaver IC, Cervoni N, Champagne FA, et al. Epigenetic programming by maternal behavior. *National Neuroscience.* 2004;7(8):847-854.
93. Melas PA, Rogdaki M, Lennartsson A, et al. Antidepressant treatment is associated with epigenetic alterations in the promoter of P11 in a genetic model of depression. *International Journal of Neuropsychopharmacology* 2012;15(5):669-679.
94. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: Combining elements of clinical effectiveness and implementation research to enhance public health impact. *Medical Care.* 2012;50:217-226.
95. Glasgow RE, McKay HG, Piette JD, Reynolds KD. The RE-AIM framework for evaluating interventions: What can it tell us about approaches to chronic illness management? *Patient Education and Counseling.* 2001;44:119-127.

96. Glasgow RE, Vogt TM, Boyles SM. Evaluating the public health impact of health promotion interventions: The RE-AIM framework. *American Journal of Public Health.* 1999;89:1322-1327.
97. Rycroft-Malone J. The PARIHS framework: A framework for guiding the implementation of evidence-based practice. *Journal of Nursing Care Quality.* 2004;19:297-304.
98. Rycroft-Malone J, Kitson A, Harvey G, et al. Ingredients for change: Revisiting a conceptual framework. *Quality & Safety in Health Care.* 2002;11:174-180.
99. Hamilton M. Development of a rating scale for primary depressive illness. *British Journal of Social and Clinical Psychology.* 1967;6:278-296.
100. Asarnow JR, Jaycox LH, Duan N, et al. Effectiveness of a quality improvement intervention for adolescent depression in primary care clinics. *Journal of the American Medical Association.* 2005;293:311-319.
101. Brent D, Emslie G, Clarke G, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: The TORDIA randomized controlled clinical trial. *Journal of the American Medical Association.* 2008;299:901-913.
102. Bloomquist ML, Giovanelli A, Benton A, Piehler TF, Quevedo K, Oberstar JV. Implementation and evaluation of evidence-based psychotherapeutic practices for youth in a mental health organization. *Journal of Child and Family Studies.* in press.
103. Reynolds CR, Kamphaus RW. *The clinician's guide to the Behavior Assessment System for Children (BASC).* New York: Guilford; 2002.
104. Poznanski EO, Mokros HB. *The Children's Depression Rating Scale - Revised (CDRS-R).* Los Angeles: Western Psychological Services; 1996.
105. Beck AT, Steer RA, Brown GK. *Manual for Beck Depression Inventory, 2nd edition.* San Antonio, TX: The Psychological Corporation; 1996.
106. Guy W. *ECDEU assessment manual for psychopharmacology.* 2 ed. Washington, DC: US Government Printing Office; 1976.
107. Armsden G, Greenberg M. *Inventory of Parent and Peer Attachment (Mother, Father and Peer Version).* WA, USA: University of Washington;1989.
108. Prinz RJ, Foster S, Kent RN, O'Leary KD. Multivariate assessment of conflict in distressed and nondistressed mother-adolescent dyads. *Journal of Applied Behavior Analysis.* 1979;12:691-700.
109. Powers SI, Welsh DP. Mother-daughter interactions and adolescent girls' depression. In: Cox MJ, Brooks-Gunn J, eds. *Conflict and cohesion in families.* Mahwah, NJ: Lawrence Erlbaum Associates, Inc.; 1999:243-281.
110. Powers SI, Welsh DP, Wright V. Adolescents' affective experience of family behaviors: The role of subjective understanding. *Journal of Research on Adolescence.* 1994;4:585-599.
111. Rossello J, Bernal G. The efficacy of cognitive-behavioral and interpersonal treatments for depression in Puerto Rican adolescents. *Journal of Consulting and Clinical Psychology.* 1999;67:734-745.

112. Birmaher B, Brent DA, Kolko D, et al. Clinical outcome after short-term psychotherapy for adolescents with major depressive disorder. *Archives of General Psychiatry.* 2000;57:29-36.
113. Cheung AH, Zuckerbrot RA, Jensen PS, et al. Guidelines for adolescent depression in primary care (GLAD-PC): II. Treatment and ongoing management. *Pediatrics.* 2007;120(5):1313-1326.
114. Shaffer D, Gould MS, Brasic J, Ambrosini P, Bird HR, Aluwahlia S. A children's Global Assessment Scale (CGAS). *Archives of General Psychiatry.* 1983;40:1228-1231.
115. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C–CASA): Classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. . *American Journal of Psychiatry.* 2007;164:1035-1043.
116. Williams JB. A structured interview guide for the Hamilton Depression Rating Scales. *Archives of General Psychiatry.* 1988;45:742-747.
117. Meyers K, Winters NC. Ten-year review of rating scales II: Scales for internalizing disorders. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2002;41:634-659.
118. Kaufman J, Birmaher B, Brent D, Rao U. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry.* 1997;36:980-988.
119. Klein RG, Abikoff H, Barkley RA. Clinical trials in children and adolescents. In: Prien RF, Robinson DS, eds. *Clinical evaluation of psychotropic drugs: Principles and guidelines.* New York: Raven Press; 1994:501-546.
120. Robin AL, Foster SL. *Negotiating parent-adolescent conflict: A behavioral-family systems approach.* New York: Guilford; 1989.
121. Welsh DP, Dickson JW. Video-recall procedures for examining subjective understanding in observational data. *Journal of Family Psychology.* 2005;19:62-71.
122. Curry J, Rohde P, Simons A, et al. Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). *Journal of the American Academy of Child and Adolescent Psychiatry.* 2006;45:1427-1239.
123. Little SA, Garber J. Interpersonal and achievement orientations and specific stressors predicting depressive and aggressive symptoms in children. *Cognitive Therapy and Research.* 2000;24:651-670.
124. Lewis CC, Simons AD, Silva SG, et al. The role of readiness to change in response to treatment of adolescent depression. *Journal of Consulting and Clinical Psychology.* 2009;77:422-428.
125. McConnaughy EA, Prochaska JO, Velicer WF. Stages of change in psychotherapy: Measurement and sample profiles. *Psychotherapy: Theory, Research and Practice.* 1983;20:368-375.

126. Ascher BH, Farmer EMZ, Burns BJ, Angold A. The child and adolescent services assessment (CASA): Description and psychometrics. *Journal of Emotional and Behavioral Disorders.* 1996;4:12-20.
127. Mufson L, Clougherty K, Young JF, Verdeli H. IPT-A Supervision Checklist. In. New York, NY: Columbia University; 2004.
128. McLeod BD, Weisz JR. The therapy process observational coding system for child psychotherapy strategies scale. *Journal of Clinical Child and Adolescent Psychology.* 2010;39:436-443.
129. McLeod BD, Smith MM, Southam-Gerow MA, Weisz JR, Kendall PC. Measuring treatment differentiation for implementation research: The Therapy Process Observational Coding System for Child Psychotherapy Revised Strategies Scale. *Psychological Assessment.* 2015;27:314-325.
130. Larsen DL, Attkisson CC, Hargreaves WA, Nguyen TD. Assessment of client/patient satisfaction: Development of a general scale. *Evaluation and Program Planning.* 1979;2:197-207.
131. Rye M, Torres EM, Friborg O, Skre I, Aarons GA. The Evidence-based Practice Attitude Scale-36 (EBPAS-36): A brief and pragmatic measure of attitudes to evidence-based practice validated in US and Norwegian samples. *Implementation Science.* 2017;12:44.
132. Helfrich CD, Li YF, Sharp ND, Sales AE. Organizational readiness to change assessment (ORCA): Development of an instrument based on the promoting action of research in health services (PARIHS) framework. *Implementation Science.* 2009;4:38.
133. Hankin BL, Abramson LY, Moffitt TE, Silva PA, McGee R, Angell KE. Development of depression from preadolescence to young adulthood: Emerging gender differences in a 10-year longitudinal study. *Journal of Abnormal Psychology.* 1998;107:128-140.
134. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Archives of General Psychiatry.* 2006;63:323-329.
135. American Academy of Child and Adolescent P. Summary of the practice parameters for the assessment and treatment of children and adolescents with suicidal behavior. *J Am Acad Child Adolesc Psychiatry 37(10 Suppl):63S-83S.* 2001;40(4):495-499.
136. Almirall D, Nahum-Shani I, Sherwood NE, Murphy SA. Introduction to SMART designs for the development of adaptive interventions: With application to weight loss research. *Translational Behavioral Medicine.* 2014;4:260-274.
137. Collins LM, Murphy SA, Bierman KA. A conceptual framework for adaptive preventive interventions. *Prevention Science.* 2004;5:185-196.
138. Nahum-Shani I, Qian M, Almirall D, et al. Experimental design and primary data analysis methods for comparing adaptive interventions. *Psychological Methods.* 2012;17(4):457-477.
139. Boos DD, Stefanski LA. *Essential statistical inference: theory and methods.* New York: Springer; 2013.

140. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. *American Journal of Epidemiology.* 2008;168(6):656-664.
141. Orellana L, Rotnitzky A, Robins JM. Dynamic regime marginal structural mean models for estimation of optimal dynamic treatment regimes. *The International Journal of Biostatistics.* 2010;6(2).
142. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second panel on cost-effectiveness in health and medicine. *JAMA.* 2016;316:1093-1103.
143. Chakraborty B. Dynamic treatment regimes for managing chronic health conditions: A statistical perspective. *American Journal of Public Health.* 2011;101(1):40.
144. Chakraborty B, Murphy S, Stretcher V. Inference for non-regular parameters in optimal dynamic treatment regimes. *Statistical Methods in Medical Research.* 2009:1-27.
145. Henderson R, Ansell P, Alshibani D. Regret-regression for optimal dynamic treatment regimes. *Biometrics.* 2010;66(4):1192-1201.
146. Moodie EE, Chakraborty B, Kramer MS. Q-learning for estimating optimal dynamic treatment rules from observational data. *Canadian Journal of Statistics.* 2012;40(4):629-645.
147. Moodie EE, Platt RW. Estimating response-maximized decision rules with applications to breastfeeding. *Journal of the American Statistical Association.* 2009;104(485).
148. Moodie EE, Richardson TS, Stephens DA. Demystifying optimal dynamic treatment regimes. *Biometrics.* 2007;63(2):447-455.
149. Murphy SA, Lynch KG, Oslin D, McKay JR, TenHave T. Developing adaptive treatment strategies in substance abuse. *Drug and Alcohol Dependence.* 2007;88(S24-S30).
150. Murphy SA, Oslin DW, Rush AJ, Zhu J. Methodological challenges in constructing effective treatment sequences for chronic psychiatric disorders. *Neuropsychopharmacology.* 2007;32(2):257-262.
151. Nahum-Shani I, Qian M, Almirall D, et al. Q-learning: A data analysis method for constructing adaptive interventions. *Psychological Methods.* 2012;17(4):478-494.
152. Rosthøj S, Fullwood C, Henderson R, Stewart S. Estimation of optimal dynamic anticoagulation regimes from observational data: a regret-based approach. *Statistics in Medicine.* 2006;25(24):4197-4215.
153. Thall PF, Milikan RE, Sung HG. Evaluating multiple treatment courses in clinical trials. *Statistics in Medicine.* 2000;19(8):1011-1028.
154. Saldaña J. *The coding manual for qualitative researchers.* Thousand Oaks, CA: Sage; 2009.
155. Lencer R, Mills LJ, Alliey-Rodriguez N, et al. Genome-wide association studies of smooth pursuit and antisaccade eye movements in psychotic disorders: findings from the B-SNIP study. *Translational Psychiatry.* 2017;7(10):e1249.

156. Bishop J, Hill S, Mills LJ, et al. Genetic Analyses of Cognitive Performance in Psychotic Disorders From the Bipolar-Schizophrenia Network on Intermediate Phenotypes (BSNIP) Consortium. *Schizophrenia Bulletin.* 2017;43(1):245 - 245.
157. Chang CC, C. CC, C. TL, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience.* 2015;4:7.
158. Chen C, Zhang C, Cheng L, et al. Correlation between DNA methylation and gene expression in the brains of patients with bipolar disorder and schizophrenia. *Bipolar Disorders.* 2014;16(8):790-799.
159. Johnson WE, Li C, Rabinovic A. Adjusting batch effects in microarray expression data using empirical Bayes methods. *Biostatistics.* 2007;8(1):118-127.
160. Houseman EA, Kelsey KT, Wiencke JK, Marsit CJ. Cell-composition effects in the analysis of DNA methylation array data: a mathematical perspective. *Bioinformatics.* 2015;16:95.
161. Stevenson JM, Reilly JH, Harris MS, et al. Antipsychotic pharmacogenomics in first episode psychosis: a role for glutamate genes. *Translational Psychiatry.* 2016;6:e739.
162. Houtepen LC, ven Bergen AH, Vinkers CH, Boks MP. DNA methylation signatures of mood stabilizers and antipsychotics in bipolar disorder. *Epigenomics.* 2016;8(2):197-208.
163. Kader F, Ghai M. DNA methylation-based variation between human populations. *Molecular Genetics and Genomics.* 2017;292(1):5-35.
164. Tamayo P, Slonim D, J. M, et al. Interpreting patterns of gene expression with self-organizing maps: methods and application to hematopoietic differentiation. *Proceedings of the National Academy of Sciences of the United States of America.* 1999;96(6):2907-2912.
165. Lei, et al. A "SMART" design for building individualized treatment sequences. *Annual Review of Clinical Psychology.* 2012;8:21-48.
166. Oetting, et al. Statistical Methodology for a SMART Design in the Development of Adaptive Treatment Strategies http://dept.stat.lsa.umich.edu/~samurphy/papers/APPAPaper/APPAproof.pdf.
167. Dietz LJ, Weinberg RJ, Brent DA, Mufson L. Family-based interpersonal psychotherapy for depressed preadolescents: Examining efficacy and potential treatment mechanisms. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2015;54:191-199.
168. Gunlicks-Stoessel ML, Mufson L, Jekal A, Turner JB. The impact of perceived interpersonal functioning on treatment for adolescent depression: IPT-A versus treatment as usual in school-based health clinics. *Journal of Consulting and Clinical Psychology.* 2010;78:260-267.