SPRITES: SERTRALINE PEDIATRIC REGISTRY FOR THE EVALUATION OF SAFETY

A Non-interventional, Longitudinal, Cohort Study to Evaluate
the Effects of Long-term Sertraline Treatment in Children and Adolescents

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PROTOCOL SUMMARY

This prospective, longitudinal, cohort study is intended to evaluate the risks and benefits of up to 3 years of treatment with sertraline in subjects age 6 to 16 (inclusive).

The primary objectives are to evaluate the long-term impact of treatment with sertraline on aspects of cognition, emotional and physical development, and pubertal maturation. In order to further evaluate the relative risks and benefits of long-term sertraline exposure, a secondary objective is to evaluate the differential effect of sertraline on cognitive and emotional development and physical and pubertal maturation over time stratified by pre-specified covariates (ie, demographics, previous treatment with psychotropic medications).

A total of 900 subjects (720 exposed to sertraline as prescribed by their physician [with or without psychotherapy] and 180 exposed to psychotherapy alone) age 6 to 16 (inclusive) will be enrolled in the study. Study visits will take place at baseline, 12 weeks, 6 months, and every 6 months thereafter for 3 years. At each study visit, cognition, emotional and physical development, and pubertal maturation will be assessed using the following measures: (1) for cognition, Trails B, an objective measure of executive functioning, and the Metacognition Index from the Behavior Rating Inventory of Executive Function (BRIEF); (2) for behavioral/emotion regulation, the Behavioral Regulation Index from the BRIEF; and (3), for physical development and pubertal maturation, standardized ascertainment of height/weight and pubertal staging, eg, Tanner or Pubertal Development Scale (PDS). Sertraline exposure, reasons for dose adjustment, estimated compliance, and concomitant medications will be ascertained at each study visit. Statistical analyses will include examination of a dose-response relationship between sertraline and each outcome domain; and comparison of sertraline-exposed and unexposed subjects on each outcome domain.

Clinicians will be asked to monitor subjects closely for any indications of suicidal feelings, behavior changes, or other signs of clinical deterioration. At each study visit, adverse events (AEs), serious adverse events (SAEs), and suicidal events will be systematically assessed; SAEs will be reported to the Pfizer Safety Database, and suicidal events will be ascertained using the Columbia-Suicide Severity Rating Scale (C-SSRS).

Sertraline will be prescribed according to usual and customary “real world” practice by physicians and allied health professionals in clinical practices.

SPRITES is expected to add meaningful information on the safety of long-term sertraline use in pediatric subjects and to elucidate its potential to affect cognition, emotional and physical development, and pubertal maturation.

SCHEDULE OF ASSESSMENTS

	Study Visits							
Assessment	**Baseline[1]**	**3-month Visit**	**6-month Visit**	**12-month Visit**	**18-month Visit**	**24-month Visit**	**30-month Visit**	**36-month Visit**
Sertraline exposure[2]	X	X	X	X	X	X	X	X
Diagnoses	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Mental status (CGI-S)	X	X	X	X	X	X	X	X
Mental status (CGI-I , CGI-T, CGI-E)	NA	X	X	X	X	X	X	X
Function (CGAS)	X	X	X	X	X	X	X	X
All Adverse Events (including PAERS)[3]	X	X	X	X	X	X	X	X
Suicidal Events (C-SSRS)[3]	X	X	X	X	X	X	X	X
Serious Adverse Events (SAEs)[4]	X	X	X	X	X	X	X	X
Trails B	X	X	X	X	X	X	X	X
BRIEF (cognition)	X	X	X	X	X	X	X	X
BRIEF (behavior/emotional regulation)	X	X	X	X	X	X	X	X
HoNOSCA	X	X	X	X	X	X	X	X
Height and weight	X	X	X	X	X	X	X	X
Pubertal stage, assessed by the PDS/Tanner Staging	X	X	X	X	X	X	X	X
Selected predictor variables[5]	X	X	X	X	X	X	X	X

CGI-S=Clinical Global Impression-Severity; CGI-I=Clinical Global Impression-Improvement at post-baseline visits only; CGI-T=Clinical Global Impression-Tolerability; CGI-E=Clinical Global Impression-Effectiveness; CGAS=Child Global Assessment Schedule; PAERS=Pediatric Adverse Event Rating Scale; C-SSRS= Columbia-Suicide Severity Rating Scale; BRIEF=Behavior Rating Inventory of Executive Function; HoNOSCA=Health of the Nation Outcome Scale for Children and Adolescents; PDS=Pubertal Development Scale.

1. Baseline defined as prior to or within 45 days of initiating treatment (if exposed) and after providing parental/guardian permission and assent, when required.
2. Sertraline exposure defined by dose, duration and compliance.
3. Includes new or worsening suicidal ideation, an interrupted suicide attempt, an aborted suicide attempt, preparatory acts or behavior towards making a suicide attempt, an actual suicide attempt or completed suicide. The Baseline C-SSRS will assess lifetime risk while the C-SSRS for all other visits will assess suicidality since the subject's last visit.
4. SAEs will be reported on a by-visit basis using Pfizer's SAE reporting system and will be screened and cross-checked at study visits. For a SAE involving a suicidal event, the clinician will complete questions that comprise the SAE CRF module (SAE HARM 1, SAE HARM 2, and SAE CGI_CGAS). The clinician will ensure that a C-SSRS is completed as part of *either* a scheduled *or* unscheduled visit, but not both, and captures suicidal ideation and suicidal behavior experienced by the patient since his/her last visit.
5. For example: subject height/weight, diagnosis, comorbidity, and other potential moderators of treatment outcome.

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List of Abbreviations

AACAP	American Academy of Child and Adolescent Psychiatry
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
ASK	Antidepressant Safety in Kids Study
BRIEF	Behavior Rating Inventory of Executive Function
BMI	Body Mass Index
CAMS	Child/Anxiety Multimodal Study
CAPTN	Child and Adolescent Psychiatry Trials Network
CBT	Cognitive Behavioral Therapy
C-CASA	Columbia Classification Suicide Assessment
CGAS	Child Global Assessment Schedule
CGI	Clinical Global Impression
CGI-E	Clinical Global Impression—Effectiveness
CGI-I	Clinical Global Impression—Improvement
CGI-S	Clinical Global Impression—Severity
CGI-T	Clinical Global Impression—Tolerability
CNS	Central Nervous System
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
DCRI	Duke Clinical Research Institute
eCRF	Electronic Case Report Form
EDC SYSTEM	Electronic Data Collection System
EDP	Exposure during Pregnancy
EIU	Exposure in Utero
EMA	European Medicines Agency
FDA	Food and Drug Administration (U.S.)
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HoNOSCA	Health of the Nation Outcome Scale for Children and Adolescents
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MAR	Missing at Random

MCAR	Missing Completely at Random
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSM	Marginal Structural Model
NHANES	National Health and Nutrician Examination Survey
NHS	National Health Service
NIMH	National Institute of Mental Health
NNH	Number Needed to Harm
NNT	Number Needed to Treat
NOS	Not Otherwise Specified
OCD	Obsessive Compulsive Disorder
OTC	Over The Counter
PAERS	Pediatric Adverse Event Rating Scale
PDS	Pubertal Development Scale
PHI	Protected Health Information
PTSD	Post-Traumatic Stress Disorder
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SNRI	Serotonin Noradrenaline Reuptake Inhibitor
SPRITES	Sertraline Pediatric Registry for the Evaluation of Safety
SSRI	Selective Serotonin Reuptake Inhibitor
TADS	Treatment for Adolescents with Depression Study

1. INTRODUCTION

1.1. Overall Aim of SPRITES

The overall aim of SPRITES is to evaluate the risks and benefits of long-term sertraline treatment on cognition, emotional and physical development, and pubertal maturation in pediatric subjects. This study is a component of a post-approval regulatory commitment to the European Medicines Agency. SPRITES is intended to reflect outcomes that occur in real-world clinical practice.

1.2. Background and Rationale

In 2003, approximately 2% of children and adolescents in the United States were receiving a selective serotonin reuptake inhibitor (SSRI) antidepressant.[1, 2] Similar numbers have been reported by Zito and Safer,[3] Zito et al.,[4] Safer et al.,[5] and Olfson[6] et al for various years during the 1990s and 2000s. In preschoolers, Zito and colleagues reported that the use of antidepressants was 3.2 per 1000, or 0.3%, in 1995.[7]

In a recent review, we examined the balance between the benefits of treatment and the risk of suicidality in children and adolescents in multicenter, randomized, controlled trials of sertraline versus placebo.[8] The published literature was searched for multicenter, randomized, placebo-controlled trials of sertraline for pediatric mental disorders. Four acute-treatment trials were identified: 2 (pooled) in pediatric major depressive disorder (MDD)[9] and 2 in obsessive-compulsive disorder (OCD).[10,11] Using intent-to-treat analysis populations, we calculated the number needed to treat (NNT) for response and remission and the number needed to harm (NNH) for suicidality, and their ratio, for each clinical trial. The NNT ranged from 2 to 10, indicating clinically meaningful benefits. Benefit was greater for OCD than for MDD, and for adolescents compared with children. No age effect was apparent for OCD. Suicidality, ascertained by clinical report, was reported in 8 subjects: 5 assigned to sertraline and 3 assigned to placebo. All but 1 (a placebo-treated subject in the Pfizer, Inc. OCD trial[10]) were enrolled in the sertraline MDD trial.[12] The NNH for suicidality in MDD was 64. Treatment-emergent suicidality was more common in children (NNH 28.7) than in adolescents (NNH 706.3). Since no subject developed suicidality in sertraline-treated OCD subjects, the NNH for sertraline in OCD approaches infinity.

In December of 2008, we extended these findings in the National Institute of Mental Health (NIMH)-funded Child/Anxiety Multimodal Study (CAMS),[13] in which 488 children and adolescents with a primary diagnosis of separation anxiety disorder, generalized anxiety disorder, or social phobia were to receive 14 sessions of cognitive behavioral therapy, sertraline (at a dose of up to 200 mg per day), a combination of sertraline and cognitive behavioral therapy, or a placebo drug for 12 weeks. The percentages of children who were rated as very much or much improved on the Clinician Global Impression-Improvement (CGI-I) scale were 80.7% for combination therapy ($P < 0.001$), 59.7% for cognitive behavioral therapy ($P < 0.001$), and 54.9% for sertraline ($P < 0.001$); all therapies were superior to placebo (23.7%). Combination therapy was superior to both monotherapies ($P < 0.001$). Adverse events (AEs), including suicidal and homicidal ideation, were no more frequent in the sertraline group than in the placebo group. There were no suicidal events.

Taken together, these studies indicate a positive benefit-to-risk ratio for short-term treatment with sertraline in adolescents with MDD and in patients of all ages with anxiety and OCDs. Additionally, suicidal events appear to be more common in patients receiving sertraline for depression than for anxiety disorders or OCD.

In contrast to short-term effectiveness, the long-term impact (eg, potentially beneficial, neutral, or deleterious) of exposure to sertraline on physical, cognitive, and emotional development has not been systematically explored in the context of benefits and tolerability of sertraline in children and adolescents.

2. STUDY OBJECTIVES

This prospective cohort study will evaluate the risks and benefits of treatment with sertraline under real-world conditions in subjects age 6 to 16 (inclusive) who are prescribed sertraline by their physician for up to a 3-year period and who meet all inclusion and none of the exclusion criteria for SPRITES. Primary objectives are to evaluate the long-term impact of treatment with sertraline on cognition, emotional and physical development, and pubertal maturation. In order to further evaluate the relative risks and benefits of long-term sertraline exposure, a secondary objective is to evaluate the differential effect of sertraline on cognitive and emotional development and physical and pubertal maturation over time stratified by pre-specified covariates (ie, demographics, previous treatment with psychotropic medications).

3. STUDY DESIGN

3.1. Overview

SPRITES is a non-interventional, prospective cohort study in pediatric subjects exposed and unexposed to sertraline followed for a maximum of 3 years.

4. SUBJECT SELECTION

SPRITES will recruit 900 children age 6 to 16 (inclusive) who are exposed to sertraline (n=720) (with or without psychotherapy) and 180 exposed to psychotherapy alone under real-world conditions from approximately 50 US centers in various clinical settings, including the **C**hild and **A**dolescent **P**sychiatry **T**rials **N**etwork (**CAPTN**).

CAPTN began in 2003 as an NIMH-funded practical clinical trials network in pediatric psychiatry. Even after NIMH funding ended, the network was intended to be operational with support from the Duke Clinical Research Institute (DCRI) for the duration of SPRITES. The study includes sites that were formerly part of CAPTN and non-CAPTN sites. The overall goal of CAPTN was to evaluate the effectiveness and safety of treatments delivered under usual clinical conditions to children and adolescents with major mental illness. CAPTN specifically focused on the effectiveness of acute treatments, head-to-head comparisons of active treatments, methods for combining Cognitive Behavioral Therapy (CBT) with medication, improving partial response with adjunctive or augmentative treatments, testing adaptive treatment strategies, maintenance and discontinuation of treatment, transportability of treatments from the research to the clinical setting, moderator trials, biomarker/biosignature identification and validation, and all aspects of drug safety.

With approximately 100 investigators throughout the US and Canada plus more than fifteen child psychiatry training programs, CAPTN met the definition of a practical clinical trials network, namely real doctors treating real patients in real practice settings. Eighty percent of CAPTN investigators were in solo or group private practice; 20% were from academic centers, including those from the CAPTN training programs. SPRITES sites will include allied health professionals who will be able and willing to enroll subjects into the psychotherapy arm of the study and who will provide psychotherapy, when indicated, to subjects enrolled in the medication arm of SPRITES. CAPTN patients spanned the range of diagnoses, patterns of comorbidity, and drug and psychosocial treatments. CAPTN recently completed the Antidepressant Safety in Kids (ASK) study (NCT00395213), which informs and strongly resembles some aspects of SPRITES. The ASK study is a prospective, longitudinal, cohort "safety registry" study of predictors of benefits and AEs in 500+ youth with a depressive, anxiety, obsessive-compulsive, or eating disorder exposed to a selective serotonin reuptake inhibitor (SSRI) or serotonin noradrenaline reuptake inhibitor (SNRI).

Each SPRITES investigator will recruit approximately 20-40 subjects identified in standard clinical settings as needing treatment with sertraline. All SPRITES sites will be clinical sites such that subjects will be recruited from patients seen for clinical care within the practice. For sites with multiple investigators and/or good data quality, up to 200 subjects may be enrolled per site.

The *accessible population* is children meeting inclusion/exclusion criteria in the catchment area for the study sites. From these, the *study-eligible population* will comprise an inception cohort of enrolled subjects beginning treatment with sertraline or initiation of psychotherapy according to their clinician's practice.

To minimize attrition including unequal attrition between study groups, SPRITES will include provisions for enhancing sample maintenance adapted from attrition prevention strategies used in the Treatment for Adolescents with Depression Study (TADS). [available at https://trialweb.dcri.duke.edu/tads].

4.1. Inclusion Criteria for All Subjects

To be eligible for enrollment, the subject must meet all of the following criteria:

1. The subject and the parent must understand the nature of the study and be able to comply with protocol requirements. The parent must provide written permission and the subject must provide written assent per local IRB requirements.

2. Male or female age 6 to 16 (inclusive) on the day of parental/guardian permission/assent.

3. English-or Spanish-speaking.

4. Receiving treatment in an outpatient setting.

5. May be receiving stable treatment with another drug or psychosocial intervention except as noted in the study exclusion criteria. For this study, stability is defined as no change in dose or form of drug or psychosocial treatment for at least 2 weeks at the time of parental/guardian permission/assent. Subjects in the sertraline arm may also receive stable treatment with a psychosocial intervention (as defined above) or may begin both sertraline and a psychosocial intervention simultaneously, ie, within 2 weeks.

6. Parents/guardians must be able to complete the BRIEF, which will be offered in English and Spanish. All other treatment and study-specific assessments may be obtained independent of language if the treatment provider and the person administering the test are fluent speakers in the subject's/parent's native language.

7. Subject has no plans to move out of the area and expects to remain in contact with the treating clinic for the duration of the study.

Sertraline-Exposed Subjects only:

8. Provided a new prescription for sertraline and treatment initiated at baseline or within 45 days of enrollment in SPRITES.

9. Subject is expected to remain on sertraline beyond initial acute treatment response, defined as change from baseline.

Non-exposed Comparison Subjects only:

10. Initiating psychosocial rather than pharmacological treatment for the same spectrum of mental health diseases that would be appropriately treated with an SSRI medication on or within 45 days of enrollment in SPRITES.

11. Not taking sertraline nor have failed a trial of sertraline judged adequate in dose and duration.

4.2. Exclusion Criteria for All Subjects

The subject will not be eligible for enrollment if he or she meets any of the following criteria:

1. Subject or family is unable or unwilling to comply with the protocol.

2. In the opinion of the study investigator, subject is at high and imminent risk of a suicidal event at study entry.

3. Subject is taking an antidepressant medication other than sertraline, eg, serotonin reuptake inhibitor, serotonin norepinephrine reuptake inhibitor, serotonin norepinephrine dopamine triple reuptake inhibitor, bupropion, mirtazapine, milnacepran, monoamine oxidase inhibitor, glutaminergic modulator (such as ketamine, N-acetyl cysteine), any other marketed antidepressant medications or an

Over The Counter (OTC) antidepressant medication (such as St. John's Wort, S-adenosyl methionine, etc).

4. Subject has failed two or more trials of an SSRI where the SSRI regimen was judged to be adequate in dose and duration (defined as 8 weeks at a fluoxetine equivalent dose of 20 mg daily).

5. Subject has a current or past diagnosis of bipolar disorder, schizoaffective disorder, schizophrenia, or psychosis NOS or has a history of psychosis or is psychotic at study entry.

6. Subject has a current diagnosis of anorexia nervosa, bulimia, or eating disorder NOS.

7. Subject has a diagnosis of severe autism that would interfere with study conduct or with the interpretation of the study assessments.

8. Subject has a diagnosis of post-traumatic stress disorder.

9. Subject is receiving sertraline for a medical condition, eg, late luteal phase dysphoric disorder or other menstrual related problems, sexual problems such as premature ejaculation, or refractory syncope.

10. Subject with significant mental retardation that would interfere with study conduct or with the interpretation of the study assessments.

11. Subject has a co-occurring medical condition that (1) interferes with study participation, eg, by constraining treatment with sertraline or necessitating hospitalization or surgery, or that (2) impacts cognitive, emotional, social or physical development.

12. Subject is taking one of the following medications: a first or second generation antipsychotic, lithium, lamotrigine or other antiepileptic medication, a chronic benzodiazepine, or atomoxetine.

13. Subject is taking a psychostimulant.

14. Subject is taking a medication that has been shown to commonly cause sustained adverse effects on cognition, emotion regulation and/or growth and development.

15. Subject has a substance abuse or dependence disorder with the exception of nicotine.

16. Subject has been exposed to another investigational agent within the prior 30 days or 5 half-lives of the investigational agent, whichever is longer.

Sertraline-Exposed Subjects only:

17. Subject has demonstrated lack of benefit from or intolerance to sertraline.

18. Subject has demonstrated hypersensitivity to sertraline.

19. Subject is taking a concomitant medication for which a serious concern exists regarding an adverse drug-drug interaction with sertraline.

Non-exposed Comparison Subjects only:

20. Have failed a previous adequate course of the type of psychotherapy being considered for SPRITES within the past two years of study entry.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

SPRITES is a non-interventional study focused on the collection of subject data during clinical treatment with sertraline and/or psychosocial treatment. SPRITES does not in any way constrain the nature of the treatment administered, which, except for the requirements presented in the inclusion/exclusion criteria, is left to doctor, subject, and family preference.

Sertraline administration will be conducted in accordance with usual and customary "real world' practice at each participating site. The single safety reference document is the US Product Label[30] [see Manual of Procedures (MOP)]. While many if not most of the subjects receiving sertraline also will receive cognitive-behavioral psychotherapy, some will receive other forms of psychotherapy. For children receiving psychotherapy alone, subjects beginning any of the available forms of psychotherapy will be eligible to enroll in SPRITES.

SPRITES recommends that treatment be conducted in a fashion that is consistent with good clinical practice (GCP) recommendations as outlined in the patient information materials "Facts for Families" from the American Academy of Child and Adolescent Psychiatry (AACAP). At the option of the treating clinician, patient information materials from the AACAP "Facts for Families" series covering the use of antidepressant medications may be provided to the subject and parent and be reviewed during the parental/guardian permission/assent process.

5.2. Drug Information

Sertraline is an oral antidepressant drug of the SSRI type. Sertraline has 1 active metabolite and a lower potential for drug interactions involving CYP2D6 (hepatic cytochrome P-450 isoenzyme 2D6) than fluoxetine or paroxetine.

Sertraline was originally approved by the Food and Drug Administration (FDA) for treatment of major depressive disorder in adults, followed by treatment for OCD and panic disorder. It subsequently received approval for treatment of OCD in children age 6 or older. It has since been approved for treatment of Post Traumatic Stress Disorder (PTSD) and premenstrual dysphoric disorder, and the treatment of social anxiety disorder in adults.

5.3. Drug Supplies

All SPRITES subjects are clinical patients participating in research, thus there will be overlaps with elements of their clinical care. No drug will be supplied as part of the study; if prescribed sertraline, subjects will be receiving sertraline as they would in regular clinical care.

5.4. Concomitant Medications

Consistent with the fact that SPRITES is a non-interventional study, subjects may be receiving stable treatment at baseline with other drug (except as prohibited by the inclusion and exclusion criteria) or psychosocial interventions and may be prescribed other drug or non-drug treatment during the post-baseline course of treatment while enrolled in SPRITES.

6. STUDY PROCEDURES

6.1. Enrollment

A subject is "enrolled" into the study on the date that all eligibility criteria are confirmed. Once the SPRITES electronic case report form (eCRF) enrollment form has been completed and submitted, a unique subject number will be generated by the system and cannot be modified.

6.1.1. Duration of Enrollment

Participation in this study will be up to 3 years.

6.1.2. Screening

The clinician will first determine whether or not the subject meets the study eligibility criteria. Using the SPRITES study enrollment form, all subjects with parental/guardian permission/assent for the SPRITES study who meet all inclusion and no exclusion criteria will be entered into the eCRF. Screen Failures will not be entered into the eCRF.

6.2. Study Period

Parental/guardian permission and assent must be obtained before administration of any study-specific assessments. The schedule of assessments for the study is provided under Section: Protocol Summary.

6.2.1. Baseline Visit

For subjects receiving sertraline, the baseline visit, which will include routine clinical care and study assessments, will occur on or within 45 days of initiating treatment with sertraline and after obtaining parental/guardian permission and subject assent per local IRB requirements. For subjects in the psychotherapy group, the baseline visit will occur on or within 45 days of initiating treatment and after obtaining parental/guardian permission/assent. In addition to the study visit assessment data, the baseline assessment will

include collection of information on subject demographics, diagnosis, comorbidity, and other potential predictors of treatment outcome.

6.2.2. Post-baseline Visits

Post-baseline study assessments will be completed at any study visit whereby the subject is still "active" in the study. Active is defined as the family/subject has not withdrawn parental/guardian permission/assent or has not been lost to follow-up defined as (1) moved with no prospect of continuing in the study, ie, with no local participating center to which the subject could transfer or (2) no contact for a period of six months despite three attempts to re-contact the subject.

Post-baseline study assessments, which will include the primary and secondary study outcomes, sertraline exposure, as well as selected predictor variables, will occur at 3, 6, 12, 18, 24, 30, and 36 months. Study assessments will be timed to coincide with treatment visits insofar as is possible. Thus, clinicians are encouraged to schedule follow-up visits so that the routine visit data and study assessments for those subjects are gathered during or near the key post-baseline assessment points, as clinically indicated.

The following will be assessed:

Study Assessments

1. Sertraline exposure (defined by dose, duration, and compliance), where applicable.
2. Objective measure of executive function (Trails B).
3. Function as assessed by Child Global Assessment Schedule (CGAS).
4. Behavior Rating Inventory of Executive Function (BRIEF).
5. Health of the Nation Outcome Scale for Children and Adolescents (HoNOSCA).
6. Height and weight.
7. Pubertal development (Tanner Staging by line drawing or Pubertal Development Scale [see 7.1.4]).
8. Adverse Events/Pediatric Adverse Events Rating Scale (PAERS).
9. Columbia-Suicide Severity Rating Scale (C-SSRS).
10. For Serious Adverse Events, the following will be completed:
    i. Pfizer SAE form; and

ii. Questions that comprise the SAE Case Report Form (CRF) module (SAE HARM 1, SAE HARM 2, and SAE Clinical Global Impression (CGI)_CGAS).

Following a SAE involving a suicidal event, the clinician will ensure that a C-SSRS is completed as part of *either* a scheduled *or* unscheduled visit, but not both, and captures suicidal ideation and suicidal behavior experienced by the patient since his/her last visit.

11. Clinical Global Impression (including CGI-S, CGI-I, CGI-T, CGI-E).

12. Comprehensive assessment drawn from selected data elements from the CAPTN Core CRF.

6.2.3. Study Follow-Up

Unless parental/guardian permission/subject assent is withdrawn or the subject is lost to follow-up, he or she will be followed for the three years of the study and every attempt will be made to obtain study assessments. If a subject discontinues taking sertraline, he or she will be followed and treatment status will be documented. Likewise, if a subject in the comparison psychotherapy-treated group receives sertraline, another antidepressant, or other psychotropic medication, he or she will be followed and treatment status will be documented. Site staff should contact the subjects monthly between visits to promote study retention and assess for SAEs.

6.3. End-of-Study Form

Once a subject has completed the study by (1) exiting early due to withdrawal of parental/guardian permission/assent; (2) moving away or for some other reason being unable to participate; (3) being lost to follow-up, defined as no contact for six months; or (4) completing the full three-year study period, the database system will request a final post-study assessment. This form will summarize the study experience, contributing factors for the discontinuation (ie, medication non-compliance, adverse event) and will formally indicate that no further data for this subject are to be expected.

6.4. Withdrawal of Parental/Guardian Permission/Assent

All parents/subjects have the right to withdraw at any point during treatment without prejudice. If parental/guardian permission/assent is withdrawn, procedures performed purely for the study will stop, and the subject will be considered "inactive" for the purposes of the study. Once parental/guardian permission/assent has been withdrawn, subjects will not be eligible to "reenroll" in SPRITES.

7. OUTCOME ASSESSMENTS

7.1. Primary Outcome Assessments

Primary outcome measures will be completed for the study-specific dependent variables at specific study visits and include the following.

7.1.1. Cognitive Development

Cognitive development will be ascertained using a neuropsychological test, Trails B and the Metacognition Factor from a neurocognitive test, the BRIEF.

7.1.1.1. Objective Measure of Cognitive Function (Trails B)

Trails B, which is a set shifting task in which a person draws a line from 1 to A to 2 to B to 3 to C, etc., is widely used as a measure of executive function in children, adolescents and adults.[14-17] The subject is instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. The subject is timed as he or she connects the "trail." If the subject makes an error, and it is pointed out immediately, the subject is allowed to correct it. Errors affect the subject's score only in that the correction of errors is included in the completion time for the task. Results are reported as the number of seconds required to complete the task; therefore, higher scores reveal greater impairment. Age and gender norms are available as are cutoff scores indicating impairment.

7.1.1.2. Behavior Rating Inventory of Executive Function (BRIEF)

The Behavior Rating Inventory of Executive Function (BRIEF) is a widely used 86 item Likert style parent report measure of neurocognitive performance that includes eight theoretically and empirically derived subscales: inhibit, shift, emotional control, initiate, working memory, plan-organize, organization of materials and monitor.[18-20] These are subsumed in two broad factors: a Behavior Regulation Index consisting of the Inhibit, Shift, and Emotional Control subscales, a Metacognition Index consisting of the Working Memory, Initiate, Plan/Organize, Organization of Materials, and Task-Monitor scales. The Behavioral Regulation and Metacognition scales taken together comprise a Global Executive Composite score. The BRIEF has excellent internal consistency, test-retest reliability, inter-rater reliability, and convergent validity and is age, gender, socioeconomic status, and race/ethnicity normed.

7.1.2. Cognitive and Emotional Development

As the primary measure of cognitive function, SPRITES will employ the Metacognition Index from the BRIEF. As the primary measure of behavioral/emotion regulation, SPRITES will employ the Behavior Regulation Index from the BRIEF.

7.1.3. Height and Weight

Height, weight and body mass index will be measured and referenced to norms according to standardized procedures from the National Health and Nutrition Examination Survey (NHANES III).[21]

7.1.4. Pubertal Maturation

A crucial variable in prospective investigations of development is determination of physical and sexual maturation. In a multi-informant investigations, Dorn et al. (1990)[22] and Taylor et al. (2001)[23] found that when boys and girls were shown schematic drawings (5 ordinally-scaled drawings/photographs corresponding to the Tanner stages), their self-ratings correlated quite well with health-care-provider examination Tanner staging. To

avoid intrusiveness in examining for sexual maturity and consequent refusal to provide information on pubertal status, we will employ these self-rated pictures for teenager/adolescent self-report. In the event that the subject or parent refuses self-reported Tanner staging by line drawings and for children 12 and under, we will attempt to use the Pubertal Development Scale (PDS). The PDS is a widely used 8-item, gender-specific, self-report measure that is able to reliably ascertain pubertal status for children and adolescents age 8 to 17.[24] The PDS, which was developed for studies in which Tanner staging as a procedure is impractical, maps directly on Tanner stage as an index of pubertal development. Hence, irrespective of ascertainment we will report the outcomes for pubertal status in Tanner stage units. Specifically, if the history and physical are consistent with the subject's self report, the clinician will assign a Tanner stage rating. If they are discrepant, eg, the self-report reflects an earlier or later pubertal stage than the clinician believes is correct, the clinician will then review the self-report form with the subject and/or parent to clarify the subject's responses. This review will be done in the presence of another person, either the parent or a clinic staff member. At the end of the review, the clinician will then assign a best estimate Tanner stage rating.[1]

7.2. Secondary Outcome Assessments

Secondary outcome measures will be completed for the study-specific dependent variables at specific study visits and include the following:

- CGI-I;
- CGI-T;
- CGI-E;
- CGI-S;
- CGAS;
- HoNOSCA.

Note that the HoNOSCA provides a broad view of behavioral symptomatic and functional outcomes. Likewise, the Clinical Global Impressions scores will be "global" in nature and not specifically referenced to the symptomatic outcome of SPRITES treatment.

The NIMH CGI-S and associated CGI scales have become standard rating scales across many kinds of studies for both children and adults. The scales allow the clinician rater or independent evaluator in a clinical trial to establish both the severity of the subject's condition at baseline and the level of change over time. At baseline, the clinician rater or independent evaluator will record the severity of the subject's condition using the CGI-S,

[1] Additionally, we note that pubertal development in the U.S. begins as early as age 8 and completes as late as age 17. Based on our previous research and the demographic distribution at the CAPTN sites, we expect to be able to enroll meaningful numbers of subjects in each age stratum where the transition through puberty is operative.

which will serve as the reference score for the CGI-S, CGI-I, CGI-T, and CGI-E for all post-baseline visits.

The CGI-I scale will be used to rate improvement in the subject's condition (benefits) since baseline using the following 7-point scale: 1=very much improved, 2=much improved, 3=minimally improved, 4=not changed, 5=minimally worse, 6=much worse, 7=very much worse. *Treatment response for improvement* is defined as a CGI-I score of 1 (very much improved) or 2 (much improved), whereas *treatment nonresponse* is defined as CGI-I score of 3 to 7 (minimally improved or worse).

The CGI-T will be used to assess the tolerability of the study medication with respect to adverse events. The 7-point rating for the CGI-T will be: 1=very high, 2=high, 3=above average, 4=average, 5=low, 6=very low, and 7=extremely low.

With reference to Table 1 below, the CGI-E is scored as follows. First, the clinician rater will identify the degree of therapeutic benefit in the first column. Second, moving across the row, the clinician rater will identify the degree to which problems with tolerability adversely impact the subject. Third, having selected the terms which best describes the degrees of therapeutic benefit and adverse impact, the clinician rater will identify the cell in which benefits and adverse impacts intersect: this number will be the subject's CGI-E score. A subject who is much or very much improved and whose adverse impact rating is none or mild, ie, a CGI-E score of 1, 2, 5, or 6, will be categorized as a *responder*. All others will be categorized as *nonresponders* to study medication.

EXAMPLE: Therapeutic benefit rated as "much improved" and adverse impacts judged "No significant interference" yields a CGI-E score of 6, which indicates that this subject is a responder.

Table 1. Clinical Global Impression–Effectiveness Scoring

Therapeutic Benefit versus Tolerability/acceptability	No adverse impact	Mild adverse impact	Moderate adverse impact	Outweighs therapeutic effect
Very much improved (CGI-I=1)	1	2	3	4
Much improved (CGI-I=2)	5	6	7	8
Minimally improved (CGI-I=3)	9	10	11	12
Unchanged or worse (CGI-I ≥4)	13	14	15	16

CGI-E=Clinical Global Impression-Effectiveness
Shaded=Responder

The Children's Global Assessment Scale (CGAS), a numeric scale (1 through 100), will be used to rate the general functioning of the SPRITES study subjects.

To assess a variety of factors relevant to child mental health, SPRITES employs the clinician-rated Health of the Nation Outcome Scale for Children and Adolescents (HoNOSCA).[25]-[29] The HoNOSCA has 13 sub-scales, each rated from 0 (no problems)

through 4 (severe problems): disruptive or aggressive behavior, Attention Deficit Hyperactivity Disorder (ADHD), self-harm, substance abuse, school problems, physical illness, psychosis, physical symptoms, internalizing symptoms, peer relationships, self-care, family relationships and school attendance problems. Completed by the treating clinician using all available information, the HoNOSCA is widely used as both a clinical measure in the British National Health Service (NHS) and as a treatment outcome measure in research studies, where it shows good to excellent convergent validity, internal and test-retest reliability, and change sensitivity.

7.3. Possible Risk and Benefit of Assessments

This study is a data-collection effort designed according to a "best practice" standard of care. There are no anticipated risks of participating in the assessment portions of this study other than the risk of loss of confidentiality. Some of the questions may be considered repetitive or boring or in the case of Tanner self-report, mildly upsetting. The instruments will not replace or interfere with the treatment the subject will be receiving. Additional side effects may be detected as a result of participating in this study (although there is no way of knowing whether the standard method of evaluation would or would not have detected the same side effect).

8. ADVERSE EVENT REPORTING REQUIREMENTS

The table below summarizes the requirements for recording safety events on the electronic case report form and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These requirements apply to all participating patients. These events are defined in the section "Definitions of safety events".

Safety event	Recorded on the electronic adverse event case report form	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None

Safety event	Recorded on the electronic adverse event case report form	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" below)

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to a drug under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the electronic adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

The single reference safety document for SPRITES is the Sertraline US product label[30] (see MOP).

At each study visit, investigators will solicit any adverse events that occurred since the last study visit that meet the AE definition as described in the section below entitled Adverse Events. To support investigators in assessing for AEs that occurred since the previous study

visit, the 43 item PAERS in the eCRF will be used as described in the section below titled Pediatric Adverse Event Rating Scale (PAERS).

SPRITES will systematically collect SAEs, as described in the section below entitled Serious Adverse Events. All SAEs will be reported within 24 hours of the site being made aware of the SAE using Pfizer's standard SAE reporting system, via the Pfizer non-interventional study SAE report form along with supplemental SPRITES-specific information on the eCRF. The subject number assigned by the eCRF will be used as the subject ID on the SAE form.

The FDA recently warned the public about an increased risk of suicidal thoughts and behaviors in children and adolescents treated with antidepressant drugs, including those used in this study.[30,31] The FDA recommends closely monitoring patients who begin taking antidepressants for worsening symptoms, suicidal thoughts or feelings, and unusual changes in behavior. Families and caregivers are advised to observe the patient closely and communicate with the prescribing doctor frequently. As recommended by the FDA, the proposed study procedures ask the clinician to observe the subject closely for any indications of suicidal feelings, behavior changes, or other signs of clinical deterioration. At the initial assessment and throughout the study, psychiatric symptoms, including depressive symptoms and possible suicidal ideation (having thoughts or ideas of harming oneself), will be assessed. If the subject develops significant suicidal ideation, a preparatory or interrupted suicide attempt or makes a suicide attempt at any point during the study, the study doctor will make sure that the subject receives appropriate assessment and treatment, which may or may not include dose adjustment or discontinuation of sertraline. All such events will be classified as SAEs and will be reported immediately in two formats: First, the study clinician will complete the Pfizer SAE reporting procedure. Second, the study clinician will complete a C-SSRS and supplemental data fields on the eCRF established for this purpose. In addition to the C-SSRS and other SAE-specific information, the study clinician will also complete sections of the study visit assessment package that involve exposure to sertraline and relevant secondary outcomes, such as the CGI scores.

Reporting period

For each patient, the safety event reporting period begins at the time of the patient's informed consent and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (eg, patient changes his/her mind about participation), the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to sertraline, the SAE also must be reported to Pfizer Safety.

Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to sertraline, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that sertraline caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether sertraline caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that sertraline did not cause the event, this should be clearly documented on the electronic Adverse Event Report Form and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

Common adverse events

Adverse events that arise since the patient's previous visit will be collected at each study visit using the 43 item Pediatric Adverse Event Rating Scale (PAERS), contained in the eCRF, which was developed as an empirically derived and validated AE monitoring tool that provides coverage for common important AEs due to all major classes of Central Nervous System (CNS) active medications. The PAERS, which has been reviewed and deemed acceptable by the FDA, provides rigorous prospective identification of AEs in a Phase I-IV

clinical trial and outcomes research framework. The PAERS allows for (1) simplicity and ease of use; (2) clinical applicability to a wide variety of drug exposures; (3) frequency, severity, and subjective importance of an AE; and (4) empirically-derived, psychometrically validated item content. There are four PAERS forms: (1) a child PAERS, (2) a parent PAERS, (3) a clinician PAERS, and (4) a PAERS clinician interview form. SPRITES will use the PAERS Clinician Interview format in which the PAERs is deployed as a semi-structured interview in which the physician does a careful verbal review of all PAERS items with the child and the parent. To make the interview version of the PAERS easy to administer and to code, the PAERS Clinician Interview form includes the child probe questions as well as the MedDRA coded clinician item wording so that the interviewer uses child friendly language to ask questions while the construct being measured is captured in MedDRA terminology.

Given the extended period of time between study visits, the PAERS is a required tool that helps facilitate the investigator in ascertaining common AEs that may have occurred since the previous study visit. The PAERS eCRF will also be used to collect all AEs since the previous visit.

The PAERS clinician form covers the following domains of interest relative to each AE: presence in the past week, resolution, severity, causality, and impact on function. AE severity and AE-associated functional impairment will be tracked on a five point Likert scale: none, mild, moderate, severe, and extreme.

Serious adverse events

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute adverse events);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by Pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

Suicidal events

Suicide-related events are considered important medical events that meet the SAE reporting requirement. Suicidal events include worsening suicidal ideation, an interrupted suicide attempt, an aborted suicide attempt, preparatory acts or behavior towards making a suicide attempt, an actual suicide attempt, or completed suicide. Suicidal events like all SAEs will be recorded within 24 hours of the site staff being made aware, not only at the scheduled study visits. At each clinical visit, the study clinician will inquire about new suicidal events and complete the post-baseline version of Columbia-Suicide Severity Rating Scale (C-SSRS) to capture suicidal ideation and suicidal behavior experienced by the patient since his/her last visit.[32,33] To establish a reference baseline, the baseline and screening version of the C-SSRS will have been completed as part of the baseline visit. The C-SSRS will provide a standardized, structured framework for completing the Columbia Classification of Suicide Assessment (C-CASA) scoring, which is the FDA/European Medicines Agency (EMA) preferred classification for suicidal events. The PAERS and the HoNOSCA include suicidal ideation, suicidal behavior, and harm to others. If according to pre-defined criteria responses on the PAERS and/or the HoNOSCA there is a suggestion that an SAE may have occurred but the required SAE assessments have not been completed, the site will be queried regarding the accuracy of the SAE reporting requirement.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (eg, patient has no place to sleep);

- Administrative admission (eg, for yearly exam);
- Optional admission not associated with a precipitating medical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Protocol-specified admission during clinical study (eg, for a procedure required by the study protocol).

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (eg, environmental) sertraline, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to sertraline (maternal exposure).

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to sertraline prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with sertraline, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to sertraline in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product

by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (eg, induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (eg, inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);

- Confusion with regard to invented name (eg, trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.

- Medication errors that do not involve a patient directly (eg, potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:

- An identifiable reporter;

- A suspect product;

- The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Communication of Issues

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of sertraline, Pfizer should be informed immediately. In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this non-interventional study protocol that the investigator becomes aware of.

9. DATA ANALYSIS/STATISTICAL METHODS

9.1. Power/Sample Size Estimates

In this non-interventional study, 720 subjects will start treatment with sertraline and 180 will start with psychotherapy alone. Statistical testing will be done comparing exposure groups determined at the end of the study. Statistical power in detecting a difference between exposure groups is dependent on the type I error, the numbers of subjects in each exposure group, and the standardized difference in mean outcome between the groups.

If we consider a 2-tailed type I error equal to 0.05 and 2 groups with 180 subjects each, there would be at least 80% power to detect an absolute value of the standardized difference in means equal to or greater than 0.3 for any contrast. In other words, the detectable difference would be 0.3*SD, where SD is the standard deviation of the outcome variable within a group. For example, if SD = 1.5, then the detectable difference between means is 0.45 (0.3 x 1.5), and if SD = 2.0, it is 0.6 (0.3 x 2.0). Thus, the estimated total sample size required to ensure adequate exposure is 720 (4 x 180 sertraline-exposed groups) + 180 (sertraline non-exposed comparison group), or 900 subjects total. If final exposure groups consisted of 720 sertraline-exposed and 180 psychotherapy-exposed subjects, the comparison of sertraline- and psychotherapy-exposed subjects at the specified 4:1 allocation ratio will have 95% power to detect an absolute value of the standardized difference in means equal to or greater than 0.3.

Type I errors for individual comparisons will not take into account multiple testing.

9.2. Analysis Plan

9.2.1. Descriptive Analysis of Primary Outcome Measures

Descriptive summaries will be produced by each visit and treatment exposure for the primary outcome measures: Trails B, BRIEF Metacognition Index, BRIEF Behavioral Regulation Index, height, weight, and Tanner Scale. Body Mass Index (BMI) will also be included in these descriptive summaries.

Standardized versions of all of the primary outcome measures, with the exception of the Tanner Scale, will be analyzed as well. The BRIEF, height, weight and BMI outcome measures will be sex and age standardized via a Z-score or T-score transformation. The Trails B primary outcome measure will be standardized by age only. For height-adjusted

weight data, analysis of BMI standardized for age will be performed using measures specified by the Centers for Disease Control and Prevention.

9.2.2. Marginal Structural Model (MSM) Analysis of Primary Outcome Measures

The main questions of interest are 1) the dose-response relationship between sertraline and the primary outcome measures, and 2) the comparison between sertraline-exposed and unexposed patients. Change from baseline in Trails B, BRIEF Metacognition Index, BRIEF Behavioral Regulation Index, height, weight, BMI and Tanner Scale will be analyzed using the repeated measures mixed model via the MSM approach, in order to control for potential time-varying confounders and treatment switching during the study. Standardized outcomes will be analyzed similarly. In accordance with the MSM approach, adjustment for potential time-dependent confounding and treatment switching, as well as adjustment for missing data, will be carried out using inverse probability weighting.

1. A dose-response analysis of the relationship between sertraline exposure and each outcome will use an empirically derived (accounting for duration and compliance) continuous exposure variable, defined as average dose in mg/day, to summarize the cumulative sertraline exposure information at each visit over the 3 years of follow-up. Additional analyses will utilize recent exposure, defined at each visit as average sertraline dose (in mg/day) since last visit. These exposure variables will also be a) categorized using pre-specified dose categories, and b) dichotomized; one group defined as those with a cumulative exposure greater than zero and the other group defined as those not exposed to sertraline. The following areas of interest will be addressed:

    a. Relationship between visit-specific *cumulative* exposure (continuous) and the outcomes.

    b. Relationship between visit-specific *cumulative* exposure (categorized) and the outcomes.

    c. Relationship between visit-specific *recent* exposure (continuous) and the outcomes.

    d. Relationship between visit-specific *recent* exposure (categorized) and the outcomes.

2. An analysis of sertraline-exposed and unexposed subjects will compare mean primary outcomes at each visit between the Always versus Never Exposed to Sertraline exposure categories. Patients will be categorized according to their actual treatment exposure at baseline. Patients' outcome data will be included in the analysis up to the first missed visit or the first visit where they changed treatment as follows: a) discontinued sertraline for patients who started on sertraline at baseline, or b) were exposed to sertraline for the first time for patients who did not receive sertraline at baseline. Patients who only had baseline visit and no follow-up data will be excluded.

Estimates of the model coefficients and contrasts of interest will be presented with 95% confidence intervals. A nominal P-value will be presented. Further details on the statistical analyses can be found in the study Statistical Analysis Plan (SAP).

9.3. Methods to Control for Potential Limitations

In observational studies like SPRITES, there is no treatment randomization, and investigators assign treatment based on standard of care, eg, their clinical judgment. Therefore, to minimize the effects of potential stable confounders (ie, gender), channeling bias, time-varying confounders, treatment discontinuation and switches, and/or missing data, a MSM approach will be utilized. A MSM analysis is a weighted repeated measures approach using treatment as a time-varying covariate. Weights produce a pseudo-population with a balance in both time-invariant and time-varying covariates allowing for causal treatment comparisons using standard repeated measures models. Adjustments for missing at random (MAR) or missing completely at random (MCAR) can be incorporated directly into the proposed models.

9.4. Sensitivity Analyses

Appropriate sensitivity analyses will be performed to test the robustness of the findings for the primary analyses. Additional details can be found in the statistical analysis plan.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The DCRI will perform clinical monitoring, including review of the data within the eCRF. There will be no source document verification.

See the Clinical Monitoring Plan for additional details.

11. DATA HANDLING AND RECORD KEEPING

Clinical sites will be provided with a printed SPRITES eCRF or the capability to print copies of the eCRF, for ease of review and generation of any site-specific source document templates. SPRITES will use the InForm™ electronic data collection (EDC) system to record study data obtained from the SPRITES protocol. Additional data will be collected using the Pfizer SAE Form, and the Pfizer Exposure In Utero Supplemental Form, as applicable. Investigators will be expected to enter their study data into the eCRF database, a web-based system, customized for SPRITES in a timely manner and to report SAEs and Exposure In Utero as described in Section 8.

Before initiation of the study, each site will be contacted as to computer availability, hardware specifications, and internet connectivity, to evaluate the capacity of the site to use this type of data-collection system. The investigator's site staff entering data will receive training on the system, after which each person will be issued a unique user identification and password.

For security reasons, and in compliance with regulatory guidelines, it is imperative that only the person who owns the user identification and password access the system using his or her own unique access codes. Access codes are nontransferable. Site personnel who have not undergone training may not use the system and will not be issued user identification and password until appropriate training is completed.

12. ETHICS

12.1. Institutional Review Board/Independent Ethics Committee

The appropriate institutional review board (IRB)/independent ethics committee (IEC) must approve the protocol and parental/guardian permission/subject assent documents, agree to monitor the conduct of the study, and agree to review study progress periodically, at intervals not to exceed 1 year. The investigator will provide Pfizer, Inc. with documentation that the IRB has approved the study *before* the study may begin.

In addition, the investigator must provide the following documentation to Pfizer, Inc:

- IRB annual reapproval of the protocol, per International Conference on Harmonisation (ICH), ICH E6, the Good Clinical Practice guideline, and the ethical principles described therein that have their basis in the Declaration of Helsinki.

- IRB approval of revisions to the parental/guardian permission/subject assent documents or any amendments to the protocol. Any revisions to the protocol that may increase subject risk exposure must be approved before implementation. Administrative changes (such as a change in address or phone number) must be sent to IRBs/IECs but do not require their approval. The investigator will provide Pfizer, Inc. with documentation of all approvals.

12.1.1. Study Approval

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, parental permission/subject assent forms, and other relevant documents, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the investigator file. Copies of IRB/IEC approvals should be forwarded to Pfizer, Inc.

12.1.2. Amendments to the Protocol

Once the protocol has been approved by the local site IRB, the site investigators will not modify it. The site investigators will be notified in writing of any amendments to the protocol and/or the parental/guardian permission or subject assent form. The site investigators must obtain permission in writing from the IRB before implementing protocol amendments or parental/guardian permission or subject assent form changes.

The only circumstance in which an amendment may be initiated before IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer, Inc. in writing within 5 working days after the implementation.

The principal investigator or his or her study staff must notify the local IRB when the study is closed and provide a final report within 1 year of the last subject's completion of the study.

12.2. Ethical Conduct of the Study

The study will be conducted in compliance with 45CFR46, 21CFR50, 21CFR56, 21CFR312, 21CFR812, and 45CFR164.508-514, and in compliance with the Guidelines of the International Conference on Harmonization (ICH), to the extent required by the U.S. Food and Drug Administration.

By signing this protocol, the investigator agrees to conduct the study in compliance with the protocol, applicable standard operating procedures and/or guidelines, the ICH guidelines and the ethical principles described therein that have their basis in the Declaration of Helsinki, and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

12.3. Subject Information and parental/guardian permission/assent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures. In case of data transfer, Pfizer, Inc. will maintain high standards of confidentiality and protection of subject personal data. The parental/guardian permission/subject assent forms must be agreed to by Pfizer, Inc. and the IRB/IEC and must be in compliance with local regulatory requirements and legal requirements. The investigator must ensure that each study subject and his/her parents/guardian are fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written parental/guardian permission and assent from each subject, per local IRB requirements before any study-specific activity is performed. The parental/guardian permission and assent forms used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer, Inc. before use. The investigator will retain the original of each subject's signed assent and parental/guardian permission forms. Subjects will provide written assent as required by the local site IRB.

12.3.1. Subject Information

Each subject will be identified by a subject identification number assigned in the eCRF. Each subject ID will be an anonymous alphanumeric code. A subset of identifying information will be collected to ensure the accuracy and validity of the data and to achieve the scientific aims of the study. Specifically, the subject's age will be collected since this is an important predictor of differential response to medication. Subject initials will be collected and displayed to clinicians entering subject data into the system. This is to ensure that when a subject number is selected, the clinician can confirm that he or she is entering data for the correct subject. Other identifying information, such as the subject's name, Social Security number, or e-mail address will not be recorded on the CRF pages or within the database system.

12.3.2. Parental/guardian permission/assent

The investigator has both ethical and legal responsibility to ensure that each subject being considered for inclusion in this study is given a full explanation of the study. Written parental/guardian permission and assent, per local IRB requirements will be obtained for all subjects before any study-related assessments or procedures are performed.

Written parental/guardian permission/assent will be documented on forms approved by the same IRB responsible for approval of this protocol. The forms will conform to ICH guidelines and to the institutional requirements for parental/guardian permission/assent and applicable regulations. The investigator agrees to obtain approval from Pfizer, Inc. for any parental/guardian permission/assent form intended for use in the study, before submission for IRB approval.

The parental/guardian permission/assent forms will be reviewed with the prospective study subject and his or her parent, and the investigator or qualified designee will be available to answer questions regarding procedures, risks, and alternatives.

Once the appropriate essential information has been provided to the subject and fully explained by the investigators or qualified designee, and it is felt that the subject and parent understand the implications of participating, the subject, parent and the investigator or designee will sign and date the IRB-approved parental/guardian permission/assent forms. The subject will receive a copy of the signed forms. The original signed and dated forms will be kept in the site's regulatory file. Documentation of the parental/guardian permission/assent process for participation in this trial will be noted in the subject's medical record.

If the subject is illiterate, an additional impartial witness may be required to participate in the parental/guardian permission/assent process per local IRB requirements.

The subject or his or her parent will be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information to the subject will be documented.

12.4. Confidentiality

Subjects will be assigned a unique subject ID by which they will be identified; the key (the patient-identifying information) will be held securely at the local enrolling site and will not be transmitted to the study sponsor or to data management. However, when reporting SAEs, the site will include the unique ID, gender, and date of birth on the AE form. Investigators will be provided with electronic access to CRFs for data submission as required for each research subject and any other forms as necessary. The investigator and/or institution will:

- Maintain a study file for each subject, to include at a minimum the signed parental/guardian permission and assent (if applicable).

- Maintain current IRB approval and keep a regulatory file with copies of all IRB correspondence.

- Submit SAE forms immediately and other data according to the data schedule, to allow for reporting of SAEs to the FDA and other regulatory authorities if necessary, as well as safety analyses.

Safety data will be forwarded to the EMA and other regulatory bodies by Pfizer, Inc., per relevant regulations. No other individual subject will be identified in study reports or publications. Records may be reviewed in order to meet federal or state regulations. Upon the request of authorized personnel from Pfizer, Inc., its designees, or the FDA, or regulatory authorities from other countries, the investigator will make available for inspection source documents, ie, records of each subject who participates in this study. This information will be treated as confidential and all efforts will be made to avoid further disclosures.

All research records will be treated as confidential and will be kept in locked files. Access will be allowed only to members of the research team, institutional staff, and regulatory agencies as mandated by law. All records will be kept confidential to the extent permitted by law. Information linking subjects to their research data will be kept in locked files at study sites. In reporting the results of this study, privacy will be protected by reporting group results. Research analytic databases will be fully unlinked and de-identified in compliance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule and the Common Rule, and access to research databases for additional analyses will be in accordance with the agreement with Pfizer, Inc.

12.5. Authorization for Use and Disclosure of Protected Health Information (Health Insurance Portability and Accountability Act)

An authorization for use and disclosure of protected health information (PHI) under the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (45 CFR § 164.102 *et seq*) will be obtained from every trial subject prior to, or at the time of, enrollment. It will be presented to, and signed by, the subject at the same time as parental/guardian permission/assent. The investigator is responsible for obtaining subjects' and parent's authorizations and signatures, and for explaining the elements of the HIPAA Authorization form if necessary.

HIPAA authorization may either be a separate form or included in the parental/guardian permission/assent, dependent upon local requirements. If a separate HIPAA document is signed, the investigator will append 1 signed original of each executed HIPAA authorization to the trial subject's signed parental/guardian permission/assent and file it in the site's regulatory file. If a second copy of the signed parental/guardian permission/assent is filed in the subject's medical records, an additional copy of the signed HIPAA authorization form will be appended. Subjects will be given the other signed duplicate for their personal records.

The HIPAA authorization form will contain all elements required under the HIPAA Privacy Rule. By law, site IRB approval of the sponsor-provided authorization form for use in this study is not required, and no such approval will be sought or requested. However, Pfizer, Inc., upon request, will provide advance copies of its HIPAA authorization form to the investigator or the site's privacy board or privacy official and will work with the site to eliminate any concerns.

The investigator or the site will promptly inform Pfizer, Inc. of any restrictions on the use or disclosure of PHI of any subject to which the site or the investigator have agreed under the Privacy Rule. The investigator or the site will also promptly inform Pfizer, Inc. of any written revocation of any subject's HIPAA authorization.

12.6. Cost to Subjects

There will be no additional costs to the subject for participating in this study other than the additional time required to complete the questionnaires. No treatments will be provided as part of the study, and non-study treatment costs will be paid through whatever mechanism the subject or his or her parent normally uses for medical care (insurance, health maintenance organization, government program, self-pay, etc.).

13. DEFINITION OF END OF STUDY

The end of study is defined as last subject's last visit at the time of study termination.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer, Inc. If a study is prematurely terminated or discontinued, Pfizer, Inc. will promptly notify the investigator. After notification, the investigator must contact all participating subjects within 3 months. As directed by Pfizer, Inc., all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

Publication of study results is discussed in the Clinical Study Agreement.

The DCRI Coordinating Investigators working with the sponsor will be primarily responsible for creation, review, and submission of the primary publications and presentations relating to the major aspects of the study and approved ancillary analyses within a timely fashion after completion of the study.

The manuscript containing the overall study results will be distributed to Pfizer, Inc. for review before submission to a peer-reviewed journal, but the final contents will be at the discretion of the principal investigator. Any other manuscripts containing these data, including abstracts, will be distributed to Pfizer, Inc. before submission with a reasonable period for review. Submitted publications will conform to international standards for biomedical manuscripts, including those regarding authorship.

16. STUDY GOVERNANCE

SPRITES will be subject to IRB review and monitoring.

No study governance structure (ie, scientific advisory board or data and safety monitoring board) will be put in place, given the aims and nature of this study.

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