STATISTICAL ANALYSIS PLAN for the Final Analysis of

SPRITES: SERTRALINE PEDIATRIC REGISTRY FOR THE EVALUATION OF SAFETY (A0501093)

Revision History

Version	Date	Author(s)	Summary of Changes/Comments
1.0	March 29, 2013	PPD	Initial Version
2.0	January 17, 2020	PPD	Various formatting updates Added list of abbreviations Made sure document references 'patients' instead of 'subjects' Removed the 'Study Objectives', 'Power/Sample Size Estimates', 'Statistical Decision Rules', 'Confounders', 'Covariates' and 'Definition of Concomitant Medication Groups' Sections Updated 'Analysis Sets / Populations' and 'Definitions of Exposure Groups' Sections Listed out specific primary and secondary endpoints Included the fact that Trails-B assessments that were done for the incorrect age will not be included as part of the primary analysis Updated list of safety endpoints and gave clarity on how safety endpoints are to be analyzed Updated 'Statistical Methodology and Statistical Analyses' Section by giving more details on descriptive analyses and the MSM analyses Removed normative control analyses Added the following appendices: 'Detailed Definitions of Treatment Exposure Groups', 'References for Normalizing Primary Outcome Measures', 'Definition for Average Dose Per Day of Sertraline' and 'Definitions for C-SSRS Analyses'
2.1	February 28, 2020	PPD	Addition of analysis of C-SSRS post-baseline data
3.0	July 30, 2020	PPD	Clarified what missing data will be imputed and how it will be done. Updated the standardization of BMI to both age and gender as performed in the CDC standardization macro. Clarified that BMI is to be summarized at baseline like all other primary outcome variables. Stated that the time-varying covariates to calculate stabilized weights for missing data only should use information from the previous visit on whether or not a patient was on psychotherapy as well as whether or not a patient was on other antidepressants.

			Updated mock SAS code in Section 6.5 to have more consistent variable names with programming specifications. The mock SAS code in Section 6.5 also removes the main effect of sertraline dose as they are not necessary for the weighted repeated measures analysis. Added a sensitivity analysis to assess the impact of COVID-19 on the results of the study. Clarified fifth criteria in the definition for *Treatment Emergent Suicidal Ideation Or Behavior Relative To Baseline Visit* in Appendix 4. Added a listing will be created of detectible protocol violations. Stated that CGI and CGAS data from SAE assessments will be incorporated into summaries of CGI and CGAS data and that the worst result across all assessments corresponding to a visit will be reported for the visit. Updated the definition for suicidal behavior in Appendix 4 so that it does not use the Question 5 on the Suicidal Behavior Form. Clarified that tests of baseline data will be a test for differences between the 'Sertraline' and the 'No Pharmacologic Therapy' treatment groups. Added the 'Most Recent Treatment Exposure' definition that is to be used to summarize PAERS and SAE events. Added a section to include the fact that data on deaths and SAEs will be requested from the Pfizer Safety Database, but not summarized as part of the analysis done by the DCRI.
4.0	October 20, 2020	PPD	Updated the imputation procedure for missing treatment information in Section 6.1 to be consistent with the definition of treatment exposure since the previous visit in Appendix 1.

			Updated Section 6.5 to mention that missed visits or visits after a missed visit will not be included in the MSM analyses. Updated models used to estimate numerator densities or probabilities for the MSM analyses by not including baseline covariates. Added wording in Appendix 1 to clarify why we are imputing 'No Pharmacologic Therapy' for visits with missing treatment data.

Non-Interventional Study Protocol
A0501093

SPRITES: SERTRALINE PEDIATRIC REGISTRY FOR THE EVALUATION OF SAFETY

Statistical Analysis Plan for the Final Analysis (SAP)

Version: 4.0

Authors:

PPD

DATE: 20 October 2020

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APPENDICES

I have reviewed this SPRITES Statistical Analysis Plan for the final analysis and agree that my organization will follow it for the SPRITES Final Analysis.

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1. LIST OF ABBREVIATIONS

AE - Adverse Event
BMI - Body Mass Index
BRIEF - Behavior Rating Inventory of Executive Function
CDC - Centers for Disease Control
CGAS - Child Global Assessment Scale
CGI-E - Clinical Global Impression-Effectiveness
CGI-I - Clinical Global Impression-Improvement
CGI-S - Clinical Global Impression-Severity
CGI-T - Clinical Global Impression-Tolerability
C-SSRS - Columbia-Suicide Severity Rating Scale
DCRI - Duke Clinical Research Institute
HoNOSCA - Heath of the Nation Outcome Score for Children and Adolescents
IRB - Institutional Review Board
MEB - Medical Evaluation Board
MSM - Marginal Structural Model
OCD - Obsessive Compulsive Disorder
PAERS - Pediatric Adverse Event Rating Scale
SAE - Serious Adverse Event
SAP - Statistical Analysis Plan
SB - Suicidal Behavior
SD - Standard Deviation
SI - Suicidal Ideation

2. AMENDMENTS FROM PREVIOUS VERSION(S)

1. Updated the imputation procedure for missing treatment information in Section 6.1 to be consistent with the definition of treatment exposure since the previous visit in Appendix 1.

2. Updated Section 6.5 to mention that missed visits or visits after a missed visit will not be included in the MSM analyses.

3. Updated models used to estimate numerator densities or probabilities for the MSM analyses by not including baseline covariates.

4. Added wording in Appendix 1 to clarify why we are imputing 'No Pharmacologic Therapy' for visits with missing treatment data.

3. INTRODUCTION

SPRITES is a prospective, longitudinal, cohort study intended to evaluate the risks and benefits of up to 3 years of treatment with sertraline in patients age 6 to 16 (inclusive). This study is a component of a post-approval regulatory commitment to the European Medicines Agency.

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 941 patients (696 exposed to sertraline as prescribed by their physician [with or without psychotherapy] and 245 exposed to psychotherapy alone) age 6 to 16 (inclusive) were 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:
    a. Trails B, an objective measure of executive functioning
    b. Metacognition Index from the Behavior Rating Inventory of Executive Function (BRIEF)
2. For Emotional Development (behavioral/emotion regulation):
    a. Behavioral Regulation Index from the BRIEF
3. For Physical Development and Pubertal Maturation:
    a. Standardized ascertainment of height, weight and Body Mass Index (BMI)
    b. Pubertal staging as assessed by Tanner Staging

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 as well as a comparison of sertraline-exposed and unexposed patients on each outcome domain.

Clinicians will be asked to monitor patients 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; AEs and SAEs will be reported to the Pfizer Safety Database per Pfizer safety reporting requirements for Non-Interventional studies, 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.

4. STUDY DESIGN

A patient is enrolled for participation in this study for up to 3 years, once all eligibility criteria are confirmed.

For patients 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 patient assent per local Institutional Review Board (IRB) requirements. For patients 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 patient demographics, diagnosis, comorbidity, and other potential predictors of treatment outcome. Post-baseline study assessments will be completed at any study visit whereby the patient is still "active" in the study. Active is defined as the family/patient 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 patient could transfer or (2) no contact for a period of six months despite three attempts to re-contact the patient/parent/guardian.

Post-baseline study assessments, which will include the primary and secondary study outcomes and sertraline exposure 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 patients are gathered during or near the key post-baseline assessment points, as clinically indicated. [see schedule of events for study assessments]. Unless parental/guardian permission/patient assent is withdrawn or the patient is lost to follow-up, he or she will be followed for the three years in the study and every attempt will be made to obtain all required study assessments. If a patient discontinues taking sertraline, he or she will be followed and treatment status will be documented. Likewise, if a patient 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 patients monthly between visits to promote study retention and to assess for SAEs. Once a patient 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 and will formally indicate that no further data for this patient are to be expected. All parents/patients 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 patient will be considered "inactive" for the purposes of the study. Once parental/guardian permission/assent has been withdrawn, patients will not be eligible to "re-enroll" in SPRITES.

4.1. Study Population

A total of 941 patients (696 exposed to sertraline as prescribed by their physician [with or without psychotherapy] and 245 exposed to psychotherapy alone) age 6 to 16 (inclusive) were enrolled in the study from 2012 to 2017.

4.1.1. Analysis Populations and Analysis Datasets

There are 3 analysis populations that will be used to analyze study data. These populations are defined as follows:

1. All Patients Population: all patients included in the database who had informed consent.

2. Safety Population: the subset of the 'All Patients' population who met at least one of the following criteria: a) had an entry on the Pediatric Adverse Event Rating Scale (PAERS) Details or the SAE Harm Event/Serious Adverse Event forms; b) had an entry on the Antidepressants (ANTIDEP) or the Psychotherapy Treatment (PSYTX) forms; c) had a post-baseline C-SSRS assessment.

3. Continuous Treatment Exposure Visits Analysis Dataset: the visits for which a patient is defined as being on continuous treatment exposure are those visits where the patient is on the same treatment they were on at baseline without having been on another treatment prior to the visit. Thus, a patient will be on continuous treatment exposure for as long as they stay on their baseline treatment without changing to another type of treatment (i.e starting sertraline for a patient who was on psychotherapy only at baseline, or stopping sertraline for a patient who was on sertraline at baseline).

4. Non-COVID-19 Impacted Visits Analysis Dataset: the visits and early terminations that did not happen after April 23, 2020. On this date, a protocol administrative letter was sent out to the sites participating in the study about COVID-19 and the allowance of remote patient visits.

4.2. Definitions of Treatment Exposure Groups

There are multiple ways in which treatment exposure will be defined for this study. Brief descriptions of these definitions are as follows with further details being found in Appendix 1.

Planned Treatment Exposure at Baseline

Patients are enrolled into the study with the intent that the patient will be on either (1) sertraline (regardless of psychotherapy) or (2) psychotherapy only. Planned treatment exposure at baseline is defined as Psychotherapy Only if psychotherapy treatment was entered and sertraline treatment was not entered on the patient's demographics form. Planned treatment exposure at baseline is defined as Sertraline if sertraline treatment was entered on the patient's demographics form (regardless of the psychotherapy treatment).

Actual Treatment Exposure

What a patient is actually exposed to can be Sertraline, Other Antidepressants or No Pharmacologic Therapy. Unless noted otherwise, actual treatment exposure will be used for analysis.

Treatment Exposure Since the Previous Visit

At each follow-up visit, a patient will be assessed for what they have been exposed to since the previous visit. This type of treatment exposure is independent from what a patient may have received prior to the previous visit or what their planned treatment exposure was at baseline.

Most Recent Treatment Exposure

This definition will only be used when summarizing PAERS and SAE data. The most recent treatment corresponding to a particular PAERS or SAE event will be defined as the treatment a patient was exposed to during the calendar month prior to the calendar month of when the PAERS or SAE event occurred. If the patient was exposed to Sertraline during the calendar month prior to the calendar month of when the event occurred, then the most recent treatment will be defined as Sertraline. Otherwise, if the patient was exposed to Other Antidepressants during the calendar month prior to the calendar month of when the event occurred, then the most recent treatment will be defined as Other Antidepressants. Otherwise, the most recent treatment will be defined as No Pharmacologic Therapy.

Always vs. Never Exposed to Sertraline

This definition will only be used in the marginal structural models (MSM) analyses. Patients will be categorized according to their actual treatment exposure at baseline, as defined above. A patients' outcome data will be included in the analysis up to the first missed visit or the first visit when they discontinued or changed actual treatment with respect to sertraline as follows:

1. Discontinued sertraline for patients who started on sertraline at baseline, or
2. 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.

5. ENDPOINTS

5.1. Primary Outcome Endpoints

The primary outcome measures to be analyzed are the (a) cognitive development ascertained using the neuropsychological test Trails B, (b) cognitive development ascertained using the Metacognition Index from the neurocognitive test BRIEF (c) behavioral/emotion regulation measured by the Behavior Regulation Index from the BRIEF, (d) height, (e) weight and (f) Tanner Staging. Additionally, to address the Medical Evaluation Board's (MEB) request to provide height-adjusted weight data, analysis of BMI as an outcome measure will also be performed. All of these measures will be summarized at each of the following study visits: baseline, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months.

Data from Trails B assessments for patients who were administered the incorrect version of Trails B form for their age and who were outside of 12 months from being the correct age for the version administered will not be included in the primary analyses. These data will be included only as part of the sensitivity analyses.

5.2. Secondary Outcome Endpoints

The secondary outcome measures will be (a) Clinical Global Impression-Improvement (CGI-I), (b) Clinical Global Impression-Tolerability (CGI-T), (c) Clinical Global Impression-Effectiveness (CGI-E), (d) Clinical Global Impression - Severity (CGI-S), (e) Child Global Assessment Score (CGAS) and (f) Health of the Nation Outcome Scale for Children and

Adolescents (HoNOSCA). These measures will be summarized at each of the following study visits: 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months. In addition, the outcome measures of CGI-S, CGAS and HoNOSCA will be summarized at baseline.

All CGI or CGAS assessments taken at a given visit or since the previous visit will be identified as corresponding to the given visit. This includes CGI or CGAS assessments associated with an SAE. The final result for a given visit will be the worst observed result among the identified assessments corresponding to the visit.

5.3. Safety Endpoints

The following safety endpoints will be summarized:

- Discontinuations from the study
- C-SSRS (See Appendix 4)
- Pediatric Adverse Event Rating Scale [PAERS]
- SAEs, deaths

6. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

6.1. General conventions

All statistical tests will be 2-sided and conducted at 0.05 significance level. 95% confidence intervals and p-values, as appropriate, will be presented. Multiplicity adjustments will not be made to account for multiple statistical tests. The last follow-up visit will be defined as the last study visit where any data has been entered. All analyses will be performed using SAS Version 9.4.

Missing data will be left as missing and will not be imputed, except for missing treatment information throughout the study and missing C-SSRS Suicidal Ideation (SI) information at baseline. If a study visit has missing sertraline and other antidepressant exposure data, then the patient will be imputed as being exposed to 'No Pharmacologic Therapy' at the visit. Further details on how treatment exposure is defined are found in Appendix 1.

For the purposes of using SI information at the baseline visit as part of the Marginal Structural Model analysis of C-SSRS data or determining positive, new onset, worsening or treatment emergent SI; missing SI information over the six months previous to the baseline study visit will be imputed. The missing SI data will be imputed using SI over the lifetime of the patient. The imputed data will only be used as part of the MSM analyses and will not be used for descriptive summaries.

6.2. Baseline Summaries

Patient enrollment and follow-up will be summarized by the Planned Treatment Exposure at Baseline. All other baseline summaries will be analyzed by the Actual Treatment Exposure at Baseline. Descriptive statistics (cell counts and percentages for categorical variables; mean,

standard deviation, median, 1st quartile, 3rd quartile, minimum, and maximum for continuous variables) will be produced within the "all patients" population for the following baseline characteristics with the exception of C-SSRS:

- Demographics
- Socioeconomic status
- Psychiatric history
- Current psychiatric disorders and other co-morbidities
- Past Treatment for Primary Psychiatric Disorders
- Risk and protective factors
- Behavioral activation
- Medical history
- Concomitant Psychiatric Medications at baseline
- Primary outcome measures at baseline (BRIEF Behavioral Regulation Index, BRIEF Metacognition Index, Trails B, Height, Weight, BMI, and Tanner Staging; See also Section 5)
- Secondary outcome measures at baseline (CGI-S, CGI-I, CGI-T, CGI-E, CGAS, HoNOSCA)
- Actual SPRITES treatment exposure at baseline
- C-SSRS at baseline

Statistical tests will be conducted to determine whether differences exist in these baseline characteristics between the 'Sertraline' and 'No Pharmacologic Therapy' Actual Treatment Exposure groups defined at baseline. Fisher's Exact tests will be conducted for categorical variables and Kruskal-Wallis tests will be conducted for continuous variables. If the computation time for the Fisher's Exact test is too long for a particular categorical variable, then some categories for the variable will be combined (typically the ones with the lowest counts) to allow for a shorter computation time for the test. In such instances, a footnote will be included in the appropriate table to indicate which categories were combined.

C-SSRS results at baseline contain information on suicidal ideation (SI) and Suicidal Behavior (SB). The information collected for SI for the baseline visit includes SI across the lifetime of the patient as well as SI within the last six months prior to the baseline visit. The information for SB for the baseline visit includes only the SB across the lifetime of the patient.

Baseline descriptive summaries of C-SSRS data will be completed for only the Safety Population. The baseline descriptive summaries of C-SSRS data will include both the information collected corresponding to the entire lifetime of the patient as well as within the last six months for SI. For SB, the baseline descriptive summary will only have a summary of SB across the lifetime of the patient.

The number and percent of patients with SI and each of the SI level categories will be reported over all patients in the Safety Population and by the actual treatment exposure category at baseline. The same will be done for SB and the type of SB, including whether there was self-injurious behavior with no suicidal intent or unknown intent.

Fisher Exact Tests will be conducted to test for differences across treatment exposure groups based on the actual treatment received at baseline.

Protocol violations are not captured systematically in the SPRITES clinical database. However, some protocol violations are detectable from other data that is entered. A listing of these detectable protocol violations will be created to assess protocol adherence. Since not all protocol violations can be detected in the SPRITES clinical database, the listing will not provide a complete assessment of protocol adherence.

6.3. 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 Staging. BMI will also be included in these descriptive summaries. The descriptive summaries for the baseline visit will use the Actual Treatment Exposure at baseline categories. The descriptive summaries for the follow-up visits will use Treatment Exposure Since the Previous Visit categories. All follow-up visits will have a summary, including the Month 3 visit.

Also, all of the primary outcome measures, with the exception of Tanner Staging, will be standardized. BMI will also be standardized 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. Details on the standardization methods to be used are found in Appendix 2. All primary outcome measures, with the exception of Tanner Staging, as well as BMI, will be summarized using non-standardized results as well as standardized results.

For all of the primary outcome measures except for Tanner Staging, the descriptive summaries will present the mean, standard deviation, median,1st quartile, 3rd quartile, minimum, and maximum. The descriptive summaries for Tanner Staging will present the number and percent of patients by Tanner Staging category.

For each of the follow-up visits, the change in a patient's value from their baseline value will be calculated for both the non-standardized and standardized results. The changes from the baseline values will then be summarized using the mean, standard deviation, median,1st quartile, 3rd quartile, minimum, and maximum. This will be done for all outcome measures with the exception of Tanner Staging.

Tanner Staging changes from the baseline values will be assessed and summarized utilizing shift tables that will display the summary of individual patient changes in Tanner Staging throughout the 36 month follow-up period of the study.

All of these descriptive summaries will be performed within the All Patients population and Continuous Treatment Exposure Visits analysis dataset. Missing data will be left as missing and will not be imputed for these descriptive summaries.

6.4. Descriptive Analysis of Post-Baseline C-SSRS Data

All post-baseline summaries of C-SSRS data will only include patients in the Safety Population and patients with missing C-SSRS data will not be included in the appropriate data summary.

Post-baseline C-SSRS data will be summarized based on if there was SI or SB at any time during follow-up. This will be done over all patients in the Safety Population and by the actual treatment exposure category at baseline.

Post-baseline C-SSRS data will also be summarized at each visit during follow-up. All C-SSRS assessments taken at a given visit or since the previous visit will be identified. This includes C-SSRS assessments associated with an SAE or an unplanned assessment. The result for each data element of the C-SSRS assessment (SI or SB) will be the worst observed result among the identified assessments corresponding to a given visit.

The C-SSRS data at a given visit will be summarized over all patients in the Safety Population who have a C-SSRS assessment during that visit as well as by the treatment exposure category they were exposed to since the previous visit.

The C-SSRS data at each post-baseline visit will be evaluated to see if there was a new onset of SI or SB. The data at each visit will also be evaluated to see if there was worsening of SI or SB. These results will also be summarized at each visit over all patients in the Safety Population who have a C-SSRS assessment during that visit and at the baseline visit as well as by the treatment exposure category they were exposed to since the previous visit.

The positive, new onset or worsening SI or SB data will also be summarized separately in patients who did and did not switch treatment after baseline. In patients who switched treatment after baseline, these data will be summarized by whether the result of a positive, new onset or worsening SI or SB occurred prior to, at or after the visit where a patient first switched treatment after baseline.

No formal statistical tests will be conducted as part of the post-baseline descriptive summaries. The MSM analysis of C-SSRS data will assess relationships between sertraline exposure and C-SSRS results over time (See Section 6.8 Marginal Structural Model Analysis of Safety Measures).

Details on the definitions for SI, SB, positive, new onset, worsening and treatment emergent C-SSRS results are found in Appendix 4 along with how it will be determined that C-SSRS data is missing.

6.5. Marginal Structural Model Analysis of Primary Outcome Measures

Change from baseline in Trails B, BRIEF Metacognition Index, BRIEF Behavioral Regulation Index, height, weight, BMI and Tanner Staging will be analyzed using the MSM model. Standardized outcomes will be analyzed similarly.

Unless specified otherwise, the MSM analyses will be conducted in the "All patients" population and assessed throughout the entire 36-month follow-up. The analysis dataset will include multiple observations for each patient, with each observation corresponding to a patient's visit. Patients who only had a baseline visit and no follow-up data will be excluded. Missed visits or visits that occurred subsequent to a missed visit will also be excluded.

General MSM approach includes two steps:

(1) First, two weights need to be estimated for each patient-visit observation (visit j, j=1, …, 7). Stabilized weights will be used.

   a. One weight accounts for treatment selection ("treatment selection" weight). This weight will be calculated as a product over the visits, starting from baseline and up to visit j, of the ratio of two densities (in case of continuous dose) or probabilities (in case of dose categories). The density in the numerator will be estimated using linear regression of dose at each visit on the dose at the previous visit. The density in the denominator will be estimated using linear regression of dose at each visit on the dose at the previous visit, baseline covariates and time-varying covariates. In case of dose categories, logistic regression will be used to estimate probabilities using the same approach as for densities in case of continuous dose.

   b. The second weight ("missing data" weight) accounts for potentially informative missing data from patients who missed visits. It will be constructed similarly to the first weight, except probabilities of remaining in the study will be used instead of densities of dose distribution. The final weight for each patient-visit observation will be calculated as the product of the "treatment selection" weight and the "missing data" weight.

Independent baseline covariates in the models for all weights will include age, sex, race, current psychiatric disorders (mood disorder, obsessive compulsive disorder (OCD), anxiety disorder), history of psychotherapy, previous treatment with psychotropic medications for SPRITES-treated disorders, history of other neurological illness, history of seizures, previous treatment with psychostimulants, previous treatment with antipsychotics, baseline CGI-S, baseline C-SSRS, baseline HoNOSCA and baseline value of the outcome being analyzed (Trails B, BRIEF Metacognition Index, BRIEF Behavioral Regulation Index, height, weight, BMI, Tanner). For visits after baseline, previous sertraline dose and visit number will also be included. Time-varying covariates will include: the value of the outcome variable being analyzed at the previous visit (Trails B, BRIEF Metacognition Index, BRIEF Behavioral Regulation Index, height, weight, BMI, Tanner), CGI-S at the previous visit, C-SSRS at the previous visit and HoNOSCA at the previous visit. In addition, for the "treatment selection" weights, the covariates of

"on psychotherapy" and "on other antidepressants" will be included in the list of time-varying covariates. For the "missing data" weights, the covariates of "on psychotherapy at the previous visit" and "on other antidepressants at the previous visit" will be included in the list of time-varying covariates. Models will be assessed for convergence and any covariates that cause convergence issues such as quasi-separation may be excluded.

(2) Second, a weighted repeated measures model analysis using generalized estimating equations will be conducted. Weights that have extremely large or extremely small values, will be truncated using 1st and 99th (or 2.5th and 97.5th, if needed) percentiles of the corresponding weight distribution.

Notation:

$USUBJID_i$ = identifier for patient i

$VISITNUM_{ij}$ = study visit month associated with visit j for patient i

$OUTCHANGE_{ij}$ = change from baseline in the outcome for patient i at visit j (j=1, …, 7)

CUM_DOSE_{ij} = cumulative dose (mg/day) associated with visit j for patient i

$CUM\_DOSE\_CAT_{ij}$ = categorized version of the cumulative dose associated with visit j for patient i

$RECENT\_DOSE_{ij}$ = recent dose (mg/day) associated with visit j for patient i

$RECENT\_DOSE\_CAT_{ij}$ = categorized version of the recent dose associated with visit j for patient i

Cumulative dose at visit j (mg/day) will be calculated as the total amount of sertraline (in mg) taken by the patient between baseline and visit j, divided by the number of days between baseline and visit j. Recent dose at visit j (mg/day) will be calculated as the total amount of sertraline (in mg) taken by the patient between visits (j-1) and j, divided by the number of days between visits (j-1) and j. More specific details on how the average sertraline dose per day will be calculated and dose categories are provided in Appendix 3.

All outcomes will be modeled using repeated measures linear regression, assuming normal distribution. The distributional assumption will be checked using histograms at each visit, and transformations or alternative distributional assumptions will be used as needed. Correlation structures such as unstructured, compound symmetry and AR(1) will be considered; final correlation structure will be selected based on the QIC criterion and model convergence.

The following questions of interest will be addressed.

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

Outcomes will be modeled as a function of month associated with the visit, cumulative dose per day in mg and the interaction between month and cumulative dose. Thus, the model assumes a separate intercept and slope of the relationship for each month.

Example SAS code:

```
proc genmod data=full;  *-- "full" means all patients/all visits up to
36 months;

  class VISITNUM USUBJID ;

  weight STABWT ;  *-- stabilized weights from MSM approach ;

  model OUTCHANGE = VISITNUM VISITNUM*CUM_DOSE /

              dist=normal link=id ;

  repeated subject=USUBJID / type=AR(1) ;

run;
```

For each month, intercept and slope of the relationship will be estimated using appropriate contrasts.

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

Outcomes will be modeled as a function of month associated with the visit, cumulative dose category and the interaction between month and cumulative dose category.

Example SAS code:

```
proc genmod data=full;  *-- "full" means all patients/all visits up to
36 months;

  class VISITNUM USUBJID CUM_DOSE_CAT;

  weight STABWT ;  *-- stabilized weights from MSM approach ;

  model OUTCHANGE = VISITNUM VISITNUM*CUM_DOSE_CAT /

              dist=normal link=id ;

  repeated subject=USUBJID / type=AR(1) ;

run;
```

For each month, least squares mean difference in the outcomes between each cumulative dose category and “0 mg/day” category will be estimated.

Comparison of “some cumulative exposure” to “no cumulative exposure” to sertraline will be addressed using a similar model, where cumulative dose categories will be “0

mg/day" and ">0 mg/day". For each month, least squares mean difference in the outcomes between ">0 mg/day" and "0 mg/day" categories will be estimated.

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

   Outcomes will be modeled as a function of month associated with the visit, recent dose per day in mg and the interaction between month and recent dose. Thus, the model assumes a separate intercept and slope of the relationship for each month.

   Example SAS code:

```
proc genmod data=full;  *-- "full" means all patients/all visits up to
36 months;

  class VISITNUM USUBJID;

  weight STABWT ;  *-- stabilized weights from MSM approach ;

  model OUTCHANGE = VISITNUM VISITNUM* RECENT_DOSE /

              dist=normal link=id ;

  repeated subject=USUBJID / type=AR(1) ;

run;
```

   For each month, intercept and slope of the relationship will be estimated using appropriate contrasts.

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

   Outcomes will be modeled as a function of month associated with the visit, cumulative dose category and the interaction between month and cumulative dose category.

   Example SAS code:

```
proc genmod data=full;  *-- "full" means all patients/all visits up to
36 months;

  class VISITNUM USUBJID RECENT_DOSE_CAT;

  weight STABWT ;  *-- stabilized weights from MSM approach ;

  model OUTCHANGE = VISITNUM VISITNUM* RECENT_DOSE_CAT /

              dist=normal link=id ;

  repeated subject=USUBJID / type=AR(1) ;

run;
```

For each month, least squares mean difference in the outcomes between each recent dose category and "0 mg/day" category will be estimated.

Comparison of "some recent exposure" to "no recent exposure" to sertraline will be addressed using a similar model, where recent dose categories will be "0 mg/day" and ">0 mg/day". For each month, least squares mean difference in the outcomes between ">0 mg/day" and "0 mg/day" categories will be estimated.

5) Comparison of sertraline-exposed ("Always Exposed") and unexposed ("Never Exposed") patients.

The objective of this analysis is to compare mean outcomes at each visit between the Always vs. Never Exposed to Sertraline exposure categories. Patients will be categorized according to their actual treatment exposure at baseline, defined above. 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.

In this analysis, "treatment selection" weight at visit *j* will be calculated as a product over the visits, starting from baseline and up to visit *j*, of the ratio of probabilities of being in the patient's observed exposure group (either "Always Exposed" or "Never Exposed"). The probabilities in the numerator will be estimated using logistic regression of the observed exposure group at each visit on observed exposure group at the previous visit and baseline covariates, and the probabilities in the denominator will be estimated using logistic regression of the observed exposure group at each visit on observed exposure group at the previous visit, baseline covariates and time-varying covariates. "Missing data" weights will be constructed as described earlier.

Outcomes will be modeled as a function of month associated with the visit, "Always Exposed" (`ALWAYS=1`) vs "Never Exposed" (`ALWAYS=0`) exposure group and the interaction between these two variables.

Example SAS code:

```
proc genmod data=trimmed ; *-- visits after treatment switch excluded ;

  class VISITNUM USUBJID ALWAYS ;

  weight STABWT ;

  model OUTCHANGE =  VISITNUM VISITNUM*ALWAYS /

              dist=normal link=id ;

  repeated subject=USUBJID / type=AR(1) ;

run;
```

For each month, least squares mean difference in the outcomes between "Always Exposed" and "Never Exposed" categories will be estimated.

Sensitivity analyses

Sensitivity analyses will be performed to evaluate the assumptions behind the MSM analyses and test the robustness of the findings of the primary analyses that utilize the MSM approach. Following Faries et al.[1], the following assumptions will be evaluated.

1. In the case of two treatments (denoted here as treatments A and B), the assumption of no unmeasured confounding, also known as the exchangeability assumption, implies that for two patients who a) have the same baseline covariates, b) have the same time-dependent covariates through visit j, c) have the same treatments through visit (j-1), and d) have *different* treatments at visit j, the potential outcome corresponding to treatment A (say) at visit j does not depend on the actual treatment received at visit j, i.e. the potential outcome corresponding to treatment A at visit j should be the same for these two patients. This assumption will be assessed using the approach by Brumback and colleagues[2]. Briefly, this method uses an unmeasured confounding function α, defined as a difference in the a) potential outcome at visit j given observed baseline covariates, observed time-dependent covariates up to visit j and observed treatment up to visit j, and b) potential outcome at visit j given observed baseline covariates, observed time-dependent covariates up to visit j, observed treatment up to visit (j-1) AND treatment at visit j, opposite to the observed treatment at that visit. In practice, constant function α is usually used. The analysis proceeds by calculating an "adjusted" outcome for each patient and each visit j by subtracting from the observed outcome a sum over visits t (t = 1, …, j) of quantities $c_t p_t$, where $c_t = \alpha$ if observed treatment at visit t was treatment A, $c_t = -\alpha$ if observed treatment at visit t was treatment B and p_t is the probability of receiving treatment opposite to the observed treatment at visit t, calculated as a function of baseline and time-dependent covariates up to visit t and observed treatment up to visit (t-1). For implementation in this study, treatment A will be any non-zero dose category (or "Always Exposed" in the analysis 5) and treatment B will be "0 mg/day" category (or "Never Exposed" in the analysis 5). For different values of α, adjusted outcomes are analyzed using MSM methodology and the results are compared with the results of the primary analysis. The goal is to find a value of α that reverses the study conclusions (i.e. results in a $p>0.05$ if the original study result was $p<0.05$).

2. Assumption of positivity will be evaluated by generating predicted probabilities for each dose category using each observed set of covariates. The goal of this analysis is to check that no observed combination of the covariates results in an estimated probability equal to 0 or 1 for any dose category, which would indicate perfect confounding.

3. The appropriateness of the weighting models will be assessed by adding interactions and nonlinear terms to the models to evaluate the impact of these modifications on the analysis results.

6.6. Subgroup Analyses

One of the secondary objectives mentioned in the protocol 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 (i.e, demographics, previous treatment with psychotropic medications). To address this objective, MSM analyses will be repeated, where weighted repeated measures models for the outcomes will additionally include terms for the subgroup and interactions between the subgroup and the terms for sertraline exposure. Using this approach, the differential effect of sertraline on the outcomes will be evaluated by the following subgroup variables, evaluated at baseline:

- Age (6-11 years old; 11-17 years old)
- Sex (Male; Female)
- Race (White; Combined Asian, Black or African American, Other, Multiple)
- Mood disorder diagnosis at baseline (yes; no)
- OCD diagnosis at baseline (yes; no)
- Anxiety disorder diagnosis at baseline (yes; no)
- Prior psychotherapy (yes; no)
- Previous treatment with psychotropic medications for SPRITES-treated disorders (yes; no)
- History of other neurological illness (yes; no)
- History of seizures (yes; no)
- Past treatment: Antipsychotics (yes; no)
- Past treatment: Psychostimulants (yes; no)

These subgroup analyses will be performed only if the overall effect of sertraline is found for a given outcome.

6.7. Safety Summaries

Safety summaries will be descriptive and performed within the safety population for the following parameters:

- Discontinuations from the study
- C-SSRS, by visit and therapy exposure category (See Appendix 4)
- PAERS by visit and therapy exposure category
- Serious Adverse Events (SAEs)
- Deaths

Continuous variables will be summarized using the mean, standard deviation, median,1st quartile, 3rd quartile, minimum, and maximum. Categorical variables will be summarized by reporting the number and percent of patients within a given category.

Deaths and discontinuations from the study will be summarized by the Planned Treatment Exposure at Baseline. Baseline summaries of C-SSRS data will define treatment exposure using the Actual Treatment Exposure at baseline. Summaries of C-SSRS data at follow-up visits will define treatment exposure using the Treatment Exposure Since the Previous Visit. Summaries of

PAERS and SAEs will be by the Most Recent Treatment. See Section 4.2 and Appendix 1 for further details on treatment exposure group definitions.

The safety data can be reported at any time during the trial and not just at study visits. Since summaries of safety data need to be tied to study visits, the study visit that an observation of safety data corresponds to will need to be determined. For the PAERS, SAE and death data, the corresponding study visit will be the study visit that is closest to the time of the PAERS, SAE or death event. This closest visit is defined as the closest visit subsequent to the onset date of the PAERS, SAE or death event. If the onset date is on the date of a visit, then the closest visit will be the visit for which the onset date is the same as the visit date. If there are no visits at or subsequent to the onset date of the PAERS, SAE or death event, then the closest visit will be the most recent visit previous to the onset date of the event. Details on how C-SSRS assessments are tied to study visits are found in Appendix 4.

6.7.1. Requests for Death and Serious Adverse Event Tables From the Pfizer Safety Database

The Pfizer safety database, Argus, serves as a repository for adverse event reporting. Adverse Event and Serious Adverse Event tables will be summarized upon Pfizer team request of listings or tables from the Argus safety database. These tables will include data on serious adverse events, exposure during pregnancy, death and non-serious reportable adverse events. This data will not be summarized or used as part of the final analysis completed by the Duke Clinical Research Institute (DCRI).

6.8. Marginal Structural Model Analysis of Safety Measures

The C-SSRS outcome of a positive or worsening Suicidal Ideation or Behavior (SI or SB) will be the only safety information that will be analyzed using the MSM model. This analysis will be conducted in the "Safety" population and assessed throughout the entire 36-month follow-up. The analysis dataset will include multiple observations for each patient, with each observation corresponding to a patient's visit. All instances of positive or worsening SI or SB will be included in the model. If multiple instances of positive or worsening SI or SB occur at the same visit, all such instances will be considered as a single instance for that visit in the model.

Patients who only had baseline visit and no follow-up data will be excluded. If a patient's baseline SI data is missing, then the SI across the lifetime of the patient, if it is available, will be used for the baseline SI data.

The same general MSM approach that was used for the primary outcome measures will also be used for the MSM analysis of the outcome of a positive or worsening SI or SB. However, the only question of interest that will be addressed will be the comparison of sertraline-exposed ("Always Exposed") and unexposed ("Never Exposed") patients. In this "Always Exposed" vs. "Never Exposed" analysis, assessments of SI and SB that occur after a patient switches treatment will not be included in the analysis.

Example SAS code:

```
proc genmod data=trimmed ; *-- visits after treatment switch excluded ;
```

```
  class VISITNUM USUBJID ALWAYS ;

  weight STABWT ;

  model CSSRS =  VISITNUM VISITNUM*ALWAYS /

              dist=bin link=logit ;

  repeated subject=USUBJID / type=AR(1) ;

run;
```

For each month, the odds ratio between "Always Exposed" and "Never Exposed" categories will be estimated. The sensitivity analysis to assess no unmeasured confounding will not be conducted for the MSM analysis of the outcome of a positive or worsening SI or SB. The reason why the sensitivity analysis will not be conducted is due to the fact that the outcome is binary. The binary outcome cannot be 'adjusted' using the approach by Brumback and colleagues[2] as the 'adjusted' outcome becomes a continuous variable that cannot be analyzed using the same MSM model structure as the original analysis. Sensitivity analyses will be performed to assess the positivity assumption and the appropriateness of the weighting models.

6.9. COVID-19 Impact Sensitivity Analysis

A sensitivity analysis will be conducted to assess the impact of COVID-19 on the final analysis. A protocol administrative letter was sent out to the sites participating in the study about COVID-19 and allowance of remote patient visits. This letter was sent to the sites on April 23, 2020.

A listing of patient visits that occurred after April 23, 2020 will be created. A listing of early terminations presumed to be due to COVID-19 will also be created. Early terminations that are presumed to be due to COVID-19 will be defined as those that occurred after April 23, 2020. Early terminations are defined as being instances where the patient ended the study prior to their 36 month visit as indicated by the 'Early Termination' form in the SPRITES clinical database.

The sensitivity analysis will be conducted by running the MSM analyses as defined in Sections 6.5 and 6.8 for the Tanner Staging outcome, the standardized primary outcomes and the C-SSRS outcome (positive or worsening SI or SB) on just the patient visits that did not occur after April 23, 2020. The sertraline dose definitions to be used to assess the dose-response relationship for this sensitivity analysis will include the continuous cumulative sertraline dose, the continuous recent sertraline dose and "always exposed" vs. "never exposed". The MSM analysis for the C-SSRS outcome will only be completed for the sertraline exposure of "always exposed" vs. "never exposed". MSM sensitivity analyses corresponding to this COVID-19 sensitivity analysis will not initially be completed, but may at a later time if deemed necessary.

The COVID-19 sensitivity analysis will also summarize any PAERS events corresponding to patient visits that did not occur after April 23, 2020.

Results from the COVID-19 sensitivity analysis will be compared against the original final analysis to determine any large differences in the results. If any large differences are seen, then exploratory analyses may be conducted to further assess the impact of COVID-19 on this study.

7. REFERENCES

1. Faries, Douglas, Andrew C. Leon, Josep Maria Haro, And Robert L. Obenchain. 2010 Analysis Of Observational Health Care Data Using Sas®. Cary, Nc: Sas Institute Inc.

2. Brumback, B.A., Hernán, M.A., Haneuse, S.J. and Robins, J.M., 2004. Sensitivity analyses for unmeasured confounding assuming a marginal structural model for repeated measures. Statistics in Medicine, *23*(5), pp.749-767.

Appendix 1. Detailed Definitions of Treatment Exposure Groups

In the SPRITES study, patients are assigned to receive either psychotherapy or prescribed sertraline at baseline based on clinical judgment and the standard of care. There is no randomization to treatment in this study. Initial baseline treatment information is entered on the Patient Demographics Form (DEMOG). Follow up information on the use of all anti-depressants, including sertraline, is found on the Antidepressants Form (ANTIDEP). Follow up information on psychotherapy visits is found on the Psychotherapy Treatment Form (PSYTX).

Definition of Planned Treatment at Baseline

Patients are enrolled into the study with the intent that the patient will be on either (1) sertraline (regardless of psychotherapy) or (2) psychotherapy only. Planned treatment exposure at baseline is defined as Psychotherapy Only if psychotherapy treatment was entered and sertraline treatment was not entered on the patient's demographics form. Planned treatment exposure at baseline is defined as Sertraline if sertraline treatment was entered on the patient's demographics form (regardless of the psychotherapy treatment).

Definition of Actual Treatment Exposure at Baseline

The definitions for whether a patient is on Sertraline Treatment, Other Antidepressants Treatment or receives No Pharmacologic Therapy at baseline are found in the following sections. Patients can be on more than one treatment at baseline.

Sertraline Treatment

A patient is defined as being on sertraline if the total daily dose at the end of the baseline visit as entered on the DEMOG form is more than 0 mg. Otherwise, the patient is defined as not being on sertraline at baseline. Patients with missing information on the total daily dose at the end of the visit as entered on the DEMOG form are defined as not being on sertraline.

Other Antidepressants Treatment

A patient is defined as being on Other Antidepressants if the first month on the ANTIDEP form for the Month 3 visit has all of the following:

1. The type of antidepressant the patient may have been taking to treat the primary symptom class is entered as something other than sertraline
2. The maximum prescribed dose for the corresponding medication and month is greater than 0
3. The number of weeks the patient was taking the corresponding medication for the month is greater than 0

Otherwise, the patient is defined as not being on an Other Antidepressant at baseline. If a patient (1) does not meet the criteria to be defined as being on an Other Antidepressant and (2) has any of the information missing which is required to determine whether or not they are on an Other Antidepressant, then they are defined as not being on an Other Antidepressant at baseline.

No Pharmacologic Therapy

If a patient is not defined as being on Sertraline or Other Antidepressants at baseline, then the patient is defined as not receiving a pharmacologic therapy at baseline.

Definition of Treatment Exposure Since the Previous Visit

The definitions for whether a patient is on Sertraline, Other Antidepressants or is not on any pharmacologic treatment at all at a post-baseline visit are found in the following sections. Patients can be on more than one treatment at a post-baseline visit. A patient will be defined as being on a treatment through the last visit where any data has been collected for a patient.

Sertraline Treatment

A patient is defined as being on Sertraline at a given visit if any month corresponding to the given visit on the ANTIDEP form has all of the following criteria met (i.e. the patient took sertraline in between the given visit and the previous visit):

1. The type of antidepressant the patient may have been taking to treat the primary symptom class is entered as sertraline
2. The maximum prescribed sertraline dose for the month is greater than 0
3. The number of weeks the patient was taking sertraline for the month is greater than 0

Otherwise, the patient is defined as not being on Sertraline at the given post-baseline visit. If a patient (1) does not meet the criteria to be defined as being on Sertraline and (2) has any of the information missing which is required to determine whether or not they are on sertraline, then they are defined as not being on Sertraline at the given post-baseline visit.

Other Antidepressants Treatment

A patient is defined as being on Other Antidepressants if any month corresponding to the given visit on the ANTIDEP form has all of the following criteria met (i.e. the patient took a non-sertraline antidepressant treatment in between the given visit and the previous visit):

1. The type of antidepressant the patient may have been taking to treat the primary symptom class is entered as something other than sertraline
2. The maximum prescribed dose for the corresponding medication and month is greater than 0
3. The number of weeks the patient was taking the corresponding medication for the month is greater than 0

Otherwise, the patient is defined as not being on an Other Antidepressant at the given post-baseline visit. If a patient (1) does not meet the criteria to be defined as being on an Other Antidepressant and (2) has any of the information missing which is required to determine

whether or not they are on an Other Antidepressant, then they are defined as not being on an Other Antidepressant at the given post-baseline visit.

No Pharmacologic Therapy

If a patient is not defined as being on Sertraline or Other Antidepressants at a post-baseline visit, then the patient is defined as not receiving a pharmacologic treatment at the post-baseline visit. The definitions for being on Sertraline or Other Antidepressants at a post-baseline visit state that a patient will not be defined as being exposed to those treatments if data is missing that is needed in order to determine whether or not a patient is on Sertraline or Other Antidepressants. Thus, post-baseline visits where treatment data is not collected will have the patient defined as not receiving a pharmacologic treatment at that visit.

Grouping of Treatment

Treatment at any specific visit will be defined according to three categories: Sertraline, Other Antidepressants and No Pharmacologic Therapy.

If a patient is defined as being on Sertraline at the specific visit, then the patient will belong to the Sertraline treatment category regardless of whether or not they are on any other treatments (e.g., other antidepressants, psychotherapy).

If a patient is defined as not taking sertraline, but they are defined as taking any other anti-depressants at the specific visit, then the patient will belong to the Other Antidepressants treatment category regardless of whether or not they are receiving psychotherapy.

If a patient is defined as not taking either sertraline or any other antidepressants at the specific visit, then the patient will belong to the No Pharmacologic Therapy treatment category. The No Pharmacologic Therapy treatment category will include patients who are on psychotherapy or not on a study treatment. If a patient has missing treatment data at a given visit, the patient will be defined as belonging to the No Pharmacologic Therapy treatment category for that visit.

The reason why post-baseline visits with missing treatment data will be defined as not receiving a pharmacologic treatment at the visit is due to how post-baseline treatment data is collected. Post-baseline treatment data is collected on the Antidepressants (ANTIDEP) form in the electronic case report form (eCRF). The form only collects information about which medications the patient is on for a given month and year since the previous visit. There is no option for the site to indicate that the patient was not on any medications except for leaving the medication information missing. Thus, if all medication data is missing, there is no way to determine whether the information is truly missing or if the patient was not on any medication. In the determination of which treatment exposure category a patient belongs to for a given visit, if the treatment information is missing for the visit, we will classify them as being on No Pharmacologic Therapy for that visit.

Appendix 2. References for Normalizing Primary Outcome Measures

Variable	Norm-adjusted Transformation	Reference
Trails B	Z-score = (actual value – normative value)/SD, based on age norms SD = Standard Deviation	Depending on age, two versions of the Trails B will be administered and therefore analyzed separately; ages 6-14 and 15 and older. 7-13 years: Anderson, V., Lajoie, G., & Bell, R. (1997). *Neuropsychology assessment of the school-aged child. Department of Psychology*. Royal Children's Hospital, Melbourne, Australia. 14 years: Knights, R.M., & Norwood, J.A. (1980). *Revised smoothed normative data on the neuropsychological test battery for children.* Unpublished. Department of Psychology, Carleton University, Ottawa, ON. 15-19 years: Tombaugh, T., N., Rees, L., & McIntyre, N. (1996). Normative data for the Trail making Test. Published in O. Spreen & E. Strauss (1998). *A compendium of neuropsychological tests*, 2nd edition. NY: Oxford University Press.
Metacognition Index from BRIEF Behavioral Rating Inventory from BRIEF	z-score based on mean raw score for T-score = 50 and SD = +/- 10. (actual value – raw score at T=50)/SD (mean SD where T=40,60), based on age & gender norms from BRIEF professional manual.	Gioia. G.A., Isquith, P.K., Guy, S.C., & Kenworthy, L. (2000). PAR: Psychological Assessment Resources, Lutz, FL.
Height Weight BMI	Z-score = (actual value – normative value)/SD, based on Centers for Disease Control (CDC) norms for age & gender	A SAS Program for the CDC Growth Charts http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm

Appendix 3. Definition for the Average Dose per Day of Sertraline

The total dose for a given month and patient is defined from data entered on the Antidepressants (ANTIDEP) form in the electronic case report form (eCRF). For a given patient and month, the observation will have dose information if any complete dose information is entered for the patient and month on the ANTIDEP form. Otherwise, the dose for a given patient and month will be 0. Dose information that is missing will be assumed to be 0. The reason for this is that the type of antidepressant that a patient may be taking for a given month can be multiple types of antidepressants. If sertraline is not selected, then it is assumed that the patient is not taking sertraline for the given month. This analysis of the average sertraline dose is only on patients who are enrolled and have data entered on the ANTIDEP form in the eCRF. It is possible that consecutive study visits for a patient may each have an observation for the same month. This happens when a study visit occurs in the middle of a month. In such cases, the monthly dose for that particular month will be calculated for each of the consecutive study visits. Then in calculation of the average dose for each study visit, only the portion of the month that falls within each study visit will be counted.

If the site indicates that the patient has taken sertraline for a given month, then the dose information (mg / month) will be taken as a function of the frequency of dosing, the maximum prescribed dose for the month, the number of weeks the patient was taking sertraline during the month and the assessment of compliance with sertraline for the month. If any of these variables are missing, then the total dose for that given month and patient will be set to zero. The formula for determining the total sertraline dose is as follows:

If the site indicates that the frequency of dosing is once per day or 'Other', then the total dose for the given patient and month is:

$$= dose * 1 * compliance * 7 * weeks$$

where

dose is the maximum prescribed dose for the month

weeks is the number of weeks the patient was taking sertraline during the month and

compliance is the results of the assessment of compliance with sertraline for the month. The assessment of compliance on the ANTIDEP form gives ranges of the percent of compliance as options to choose from. The upper limit of the range indicated by the site is what is used for the compliance results in the formula to calculate the total dose for a given patient and month.

If the site indicates that the frequency of dosing is twice per day, then the total dose for the given patient and month is:

$$= dose * 2 * compliance * 7 * weeks$$

The assumptions that are made with this formulation are as follows:

1. The 'Other' dose frequency is set to be once a day
2. The specific value for compliance is the upper end of the window indicated on the eCRF
3. Assume dose is zero if the site does not indicate that the patient is on sertraline

The average dose per day (mg / day) for a given study visit is calculated by summing up all of the total doses for a given patient across months within that study visit where the data is available and then dividing that number by the number of days since the previous study visit.

For categorical analysis, the sertraline dose will be categorized into the following categories (based on mg/day):

0
0.1 to < 25
25 to < 50
50 to < 75
75 to < 100
≥ 100

Appendix 4. Definitions for C-SSRS Analyses

The determination of a positive SI or SB as well as the determination of a new onset, worsening or treatment emergent SI or SB requires data from a given post-baseline visit to be compared to the baseline visit. For SI, the baseline results will be the information collected corresponding to the last six months prior to the baseline visit. As mentioned in Sections 6.1 and 6.8, if a patient's baseline SI data is missing, then the SI across the lifetime of the patient, if it is available, will be used for the baseline SI data. For SB, the baseline results will be the information collected corresponding to the entire lifetime of the patient.

The definitions for how to determine whether there was positive, new onset, worsening or treatment emergent SI or SB are as follows:

Positive Suicidal Ideation Or Suicidal Behavior: A patient will be considered to have a positive suicidal ideation or behavior if the patient reported no ideation and no behavior at the baseline visit and reported any suicidal ideation or behavior at the current visit. Any visit where these criteria are met will count as separate instances of positive suicidal ideation or suicidal behavior. Please note that self-injurious behavior, no suicidal intent is not considered to be suicidal ideation or behavior.

Positive Suicidal Ideation: A patient will be considered to have positive suicidal ideation if the subject reported no ideation at the baseline visit and reported any suicidal ideation at the current visit. Any visit where these criteria are met will count as separate instances of positive suicidal ideation.

Positive Suicidal Behavior: A patient will be considered to have positive suicidal behavior if the subject reported no suicidal behavior at the baseline visit and reported any suicidal behavior at the current visit. Any visit where these criteria are met will count as separate instances of positive suicidal behavior. Please note that self-injurious behavior, no suicidal intent is not considered to be suicidal behavior.

New Onset Suicidal Ideation Or Suicidal Behavior: The first post-baseline occurrence of positive suicidal ideation or suicidal behavior will be considered a new onset of suicidal ideation or behavior.

New Onset Suicidal Ideation: The first post-baseline occurrence of positive suicidal ideation will be considered a new onset of suicidal ideation.

New Onset Suicidal Behavior: The first post-baseline occurrence of positive suicidal behavior will be considered a new onset of suicidal behavior.

Worsening Suicidal Ideation Or Suicidal Behavior Relative To Baseline Visit: A patient will be considered to have a worsening of suicidal ideation or suicidal behavior if

1) The patient moved to a more severe suicidal ideation (higher numbered C-CASA ideation category; see Table 1 for details) than was reported at the baseline visit; or
2) The patient moved to a more severe suicidal behavior (lower numbered C-CASA behavior category; see Table 1 for details) than was reported at the baseline visit; or

3) The patient reports only suicidal ideation (and no suicidal behavior) at the baseline visit and reports any suicidal behavior at the current visit.

Any visit where these criteria are met will count as separate instances of worsening suicidal ideation or suicidal behavior.

Table 1. C-CASA Suicidal Ideation and Behavior Events and Codes

Event Code	Event
Suicidal Ideation	
1	Passive
2	Active: Nonspecific (no method, intent, or plan)
3	Active: Method, but no intent or plan
4	Active: Method and intent, but no plan
5	Active: Method, intent, and plan
Suicidal Behavior	
1	Completed suicide
2	Suicide attempt
3	Interrupted attempt
4	Aborted attempt
5	Preparatory actions toward imminent suicidal behaviors
Self-injurious behavior, no suicidal intent	Self-injurious behavior, no suicidal intent
Self-injurious behavior, intent unknown*	Self-injurious behavior, intent unknown

*This event is only captured on the pediatric version of the C-SSRS

Worsening Suicidal Ideation Relative To Baseline Visit: A patient will be considered to have a worsening of suicidal ideation if the patient moved to a more severe suicidal ideation (higher numbered C-CASA ideation category) than was reported at the baseline visit for patients reporting suicidal ideation at the baseline visit. Any visit where these criteria are met will count as separate instances of worsening suicidal ideation.

Worsening Suicidal Behavior Relative To Baseline Visit: A patient will be considered to have a worsening of suicidal behavior if the subject moved to a more severe suicidal behavior (lower numbered C-CASA behavior category) than was reported at the baseline visit for patients reporting suicidal behavior at the baseline visit. Any visit where these criteria are met will count as separate instances of worsening suicidal behavior.

Treatment Emergent Suicidal Ideation Or Behavior Relative To Baseline Visit: A patient will be considered to have treatment emergent suicidal ideation or suicidal behavior if the patient meets any of the following criteria:

1) Reported no suicidal ideation at the baseline visit and reports any suicidal ideation at the current visit
2) Moved to a more severe suicidal ideation (higher numbered C-CASA ideation category) than was reported at the baseline visit for patients reporting suicidal ideation at the baseline visit
3) Reported no suicidal behavior at the baseline visit and reports any suicidal behavior at the current visit
4) Moved to a more severe suicidal behavior (lower numbered C-CASA behavior category) than was reported at the baseline visit for patients reporting suicidal behavior at the baseline visit
5) Reports only suicidal ideation at the baseline visit and reports any suicidal behavior at the current visit

Treatment Emergent Suicidal Ideation Relative To Baseline Visit: A patient will be considered to have treatment emergent suicidal ideation if the patient has a new onset of suicidal ideation or a worsening of suicidal ideation, as defined above.

Treatment Emergent Suicidal Behavior Relative To Baseline Visit: A patient will be considered to have treatment emergent suicidal behavior if the subject has a new onset of suicidal behavior or a worsening of suicidal behavior, as defined above.

Maximum Post-Baseline Suicidal Ideation Or Behavior: The lowest C-CASA behavior category reported by a patient post-baseline. If no post-baseline behavior is reported, then the highest C-CASA ideation category reported post-baseline is the maximum post-baseline suicidal ideation or behavior.

Maximum Post-Baseline Suicidal Ideation: The highest C-CASA ideation category reported post-baseline.

Maximum Post-Baseline Suicidal Behavior: The lowest C-CASA behavior category reported post-baseline.

How to Determine Missing Data When Assessing Suicidal Ideation or Behavior

For the *suicidal ideation* assessment, please see the following five numbered questions:

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you wish you weren't alive anymore?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you decided how or when you would make yourself not alive anymore/kill yourself? Have you planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** ***Write response***_____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____

If a patient did not answer any of the five questions above, the patient is considered as having missing data for suicidal ideation. Otherwise, if a patient answered "Yes" to any of the five questions, the patient is considered as having suicidal ideation. Otherwise, if a patient answered "No" to both Question 1 and Question 2, and did not answer any of the other 3 questions (i.e., Questions 3, 4 and 5), the patient is considered as not having suicidal ideation. Otherwise, the patient is considered as having missing data for suicidal ideation.

For the *suicidal behavior* assessment, please see the following five questions (please note that Question 6 is for post-baseline only and the Question 5 is not used for the definition of suicidal behavior):

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
1. Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?** **Has subject engaged in Self-Injurious Behavior, intent unknown?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐ **Yes** ☐ **No** ☐
2. Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
3. Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____

4. Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
6. Completed Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

If a patient did not answer any of the questions on the Suicidal Behavior Form (Questions 1 - 4 for all visits and the inclusion of Question 6 for post-baseline visits), the patient is considered as having missing data for suicidal behavior. Otherwise, if a patient answered "Yes" on any of the five questions (four questions for baseline), the patient is considered as having suicidal behavior. Otherwise, if a patient only answered "No" to some questions and have missing data on some other questions, the patient is considered as not having suicidal behavior.

<u>How to determine whether a positive, new onset or worsening SI or SB result happened before, at or after the visit where a patient first switched from their baseline treatment</u>

The SPRITES database does not allow for the determination of exactly when SI or SB results occurred. The SI or SB results are only defined at a specific study visit and are captured from the patient's experience since the previous visit. Since positive, new onset or worsening SI or SB is defined from SI or SB results, the exact timing of those events also cannot also be determined and can only be defined at a specific study visit.

Once the study visit at which a positive, new onset or worsening SI or SB occurred is determined, the timing of a positive, new onset or worsening SI or SB relative to the first time a patient switched their treatment exposure can then be determined. The determination of treatment exposure is based on what the patient was exposed to since the previous visit.

A positive, new onset or worsening SI or SB result is determined as occurring *before* the treatment exposure switch if the study visit at which the positive, new onset or worsening SI or SB result occurred is prior to the first study visit where the patient switched treatments.

If a positive, new onset or worsening SI or SB result is determined as occurring at the same visit where the patient first switched treatments, then it cannot be determined whether the positive, new onset or worsening SI or SB result occurred before or after the treatment exposure switch since the exact timing of a SI or SB result cannot be determined within a visit. Thus, a positive, new onset or worsening SI or SB result is determined as occurring *at* the time of the treatment exposure switch if the study visit at which the positive, new onset or worsening SI or SB result occurred is the same as the first study visit where the patient switched treatments.

A positive, new onset or worsening SI or SB result is determined as occurring *after* the treatment exposure switch if the study visit at which the positive, new onset or worsening SI or SB result occurred is after the first study visit where the patient switched treatments.

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