STATISTICAL ANALYSIS PLAN

STUDY TITLE:

Clinical Trial to Evaluate the Safety and Efficacy of NRCT-101SR in Adult Attention Deficit Hyperactivity Disorder

PROTOCOL NUMBER:

[redacted]

[redacted]	NC-018
NCT#:	NCT05683249
CLIENT:	Neurocentria, Inc
IND NUMBER(S):	159057
PREPARED BY:	[redacted]

ACKNOWLEDGEMENT AND SIGNATURE SHEET

Approved:	Approved:
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Signature and Date	Signature and Date
[redacted] Oct 30, 2023	[redacted] Oct 27, 2023

VERSION HISTORY

SAP Version	Version Date	Change(s)	Rationale
1.0	2023-10-23	Initial Draft	

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LIST OF ABBREVIATIONS

List of Abbreviations

Abbreviation	Definition
AAQoL	Adult ADHD Quality of Life scale
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
AISRS	ADHD Investigator Symptom Rating Scale
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BRIEF-A	Behavior Rating Inventory Executive Function for Adults
CGI-S	Clinical Global Impression - Severity
CI	Confidence interval
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ET	Early Termination
F	Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
ICH	International Conference on Harmonization
IND	Investigational New Drug
IP	Investigational Product
ITT	Intent-To-Treat
IRT	Interactive Response Technology

Abbreviation	Definition
LC	Laboratory Classroom
LOE	Lack of Efficacy
LS	Least Squares
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Affairs
mg	Milligram
MI	Multiple Imputation
MEWS	Mind Excessive Wandering Scale
MITT	Modified Intent-To-Treat
mmHg	Millimeters of mercury
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not at Random
msec	Millisecond
PCRS	Placebo Control Reminder Script
PERMP	Permanent Product Measure of Performance
PERMP-A	Permanent Product Measure of Performance – Attempted
PERMP-C	Permanent Product Measure of Performance – Correct
PERMP-T	Permanent Product Measure of Performance – Total
PK	Pharmacokinetics
PP	Per Protocol
PROMIS-SD-SF	Patient Reported Outcomes Measurement Information System - Sleep Disturbance - Short Form
PT	Preferred Term
QTc	Corrected QT interval
RBC	Red Blood Cells
REML	Restricted Maximum Likelihood
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

Abbreviation	Definition
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

1. PURPOSE OF THE ANALYSES

This statistical analysis plan (SAP) describes the planned analysis and reporting for Protocol NC-018 (Clinical Trial to Evaluate the Safety and Efficacy of NRCT-101SR in Adult Attention Deficit Hyperactivity Disorder).

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines for statistical practice, as published by the American Statistical Association and the Royal Statistical Society.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc, or unplanned exploratory analysis performed will be clearly identified as such in the final CSR.

In preparing this SAP, the following documents were reviewed in addition to the literature references cited in this SAP:

- Clinical Research Protocol NC-018, Version 5.0 dated 27 FEB 2023
- ICH Guidance on Statistical Principles for Clinical Trials (E9)

The reader of this SAP is encouraged to also read the clinical protocol, and other identified documents, for details on the planned conduct of this study. Operational aspects relating to collection and timing of planned clinical assessments are not repeated in this SAP unless they are relevant to the planned analysis.

2. PROTOCOL SUMMARY

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-arm design, laboratory classroom (LC) trial to assess the efficacy and safety of NRCT-101SR [redacted] compared to inactive placebo over a 6-week period in approximately 216 subjects ≥ 18 years of age with Attention Deficit Hyperactivity Disorder (ADHD). The study population will include adult male and female subjects of all race/ethnicity with ADHD, recruited from sites across the US. All subjects will either be naïve to stimulant or non-stimulant ADHD medications, or prior to enrollment, have been off stimulants for at least 2 weeks and non-stimulants for at least 3 weeks.

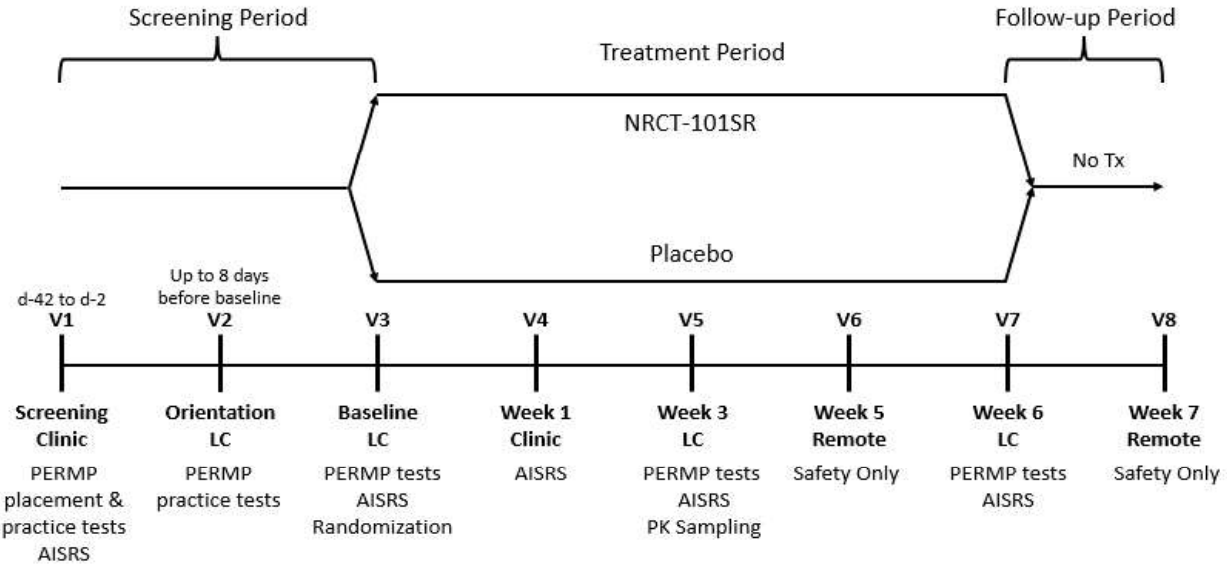
Total subject participation in the study is up to approximately 13 weeks, including a screening period (up to 6 weeks), a 6-week treatment period, and an approximate 1-week follow-up period. Each study subject will be randomized into one of two groups (1:1) to receive either active drug or placebo during the entirety of the 6-week treatment period. Within 8 days of Baseline LC visit, subjects will complete an LC Orientation Visit. At the Baseline LC visit, subjects will be randomized, assigned to a group, and dispensed study drug (first dose to be taken the next morning). The primary endpoints of the study include Permanent Product Measure of Performance (PERMP) Math Tests and the ADHD Investigator Symptom Rating Scale (AISRS). To familiarize the subjects with the PERMP, prior to the Baseline LC visit, they will complete 8 practice PERMP assessments (3 at screening and 5 at the LC Orientation visit). LC visits will be repeated at Week 3 and Week 6. Secondary and exploratory assessments will also be conducted at the Baseline, Week 3, and Week 6 LC visits. A clinic visit will be conducted at Week 1 to administer AISRS with expanded version, Hospital Anxiety and Depression Scale (HADS), and Behavior Rating Inventory Executive Function for Adults (BRIEF-A). Safety assessments (concomitant medications, adverse events [AEs], and suicide risk) will be conducted at all clinic and remote visits/phone calls (Week 5, and follow-up); safety labs will be conducted at screening, Week 3, and Week 6. For population pharmacokinetic (PK) analysis, PK sampling will be conducted at the Week 3 LC visit. Blood samples for PK will be collected prior to dosing, at 4 hours and 7 hours after dosing (with a 30-minute window). See Study Schema and Schedule of Events below.

The primary analysis will be on effects of 6-week treatment of NRCT-101SR versus placebo on performance and ADHD core symptoms in subjects with adult ADHD. The dual primary endpoints are PERMP (performance) and AISRS (core symptoms). The study will be declared successful by reaching statistical significance on either primary endpoint with adjustment for multiplicity.

Randomization will be stratified by:

- Site
- LC cohort
- Sex (approximately equal number of male and female in the study)

2.1. Study Schema



3. ANALYSIS SAMPLES

Five populations will be utilized for the analyses of data.

3.1. All Subjects Population

This includes all subjects available in the electronic data capture system and will be used to display the disposition of subjects; subjects will be presented by their randomized treatments (if applicable).

3.2. Safety Population

The Safety Population will include all subjects who receive at least one dose of study drug. Subjects will be analyzed as treated; this population will be used for reporting of safety outcomes.

3.3. Intent-to-Treat Population

The Intent-To-Treat (ITT) population will include all subjects who are randomized. Subjects will be analyzed as randomized. The ITT population is the primary population for the efficacy analyses.

3.4. Modified Intent-to-Treat Population

The Modified Intent-To-Treat (mITT) population will include all subjects who are randomized, receive at least one dose of study drug, and have at least one non-missing post-baseline efficacy measurement (PERMP-C or AISRS). Subjects will be analyzed as randomized.

3.5. Per Protocol Population

The Per Protocol (PP) population will include all subjects in the mITT population who did not incur a protocol violation that impacts the efficacy evaluation. Subjects will be analyzed as randomized.

4. ESTIMANDS FOR DUAL PRIMARY ENDPOINTS

4.1. Dual Primary Estimand #1 PERMP-C

Population

The target population is adults with ADHD as defined by the inclusion/exclusion criteria.

Variable

This primary efficacy endpoint is defined as the change from Baseline to Week 6 in mean PERMP-C score over the course of the visit (post-dose).

Intercurrent Events

A hybrid approach of treatment policy and hypothetical strategy will be used to address intercurrent events of study discontinuation. No special data handling will be used for other intercurrent events, such as subjects who initiate concomitant medications. Likewise, subjects that discontinue treatment but return for the Week 6 visit will have those data analyzed as reported. Subjects that discontinue the study due to AEs and lack of efficacy (LOE) and consequently have missing data at Week 6 are assumed to be representative of subjects that would not continue to use the drug outside of a clinical trial and their missing values following discontinuation will be imputed using multiple imputation (MI), based off the distribution of placebo values at the matching time point, conditioned on the observed data (including baseline) [redacted]. All other missing values (both intermittent and following study discontinuation) will be imputed using MI assuming that they are missing at random, conditioned on the observed data (including baseline)[redacted]. Sensitivity analyses will explore the results under different analysis assumptions.

Population-Level Summary

The population-level summary will be the difference in least-square means between treatment arms (analyzed as randomized) at Week 6 from the primary analysis model. See Section 8.1.2 for details.

4.2. Dual Primary Estimand #2 AISRS

Population

The target population is adults with ADHD as defined by the inclusion/exclusion criteria.

Variable

This primary efficacy endpoint is defined as the change from Baseline to Week 6 in AISRS score.

Intercurrent Events

A hybrid approach of treatment policy and hypothetical strategy will be used to address intercurrent events of study discontinuation. No special data handling will be used for other intercurrent events, such as subjects who initiate concomitant medications. Likewise, subjects that discontinue treatment but return for the Week 6 visit will have those data analyzed as

reported. Subjects that discontinue the study due to AEs and LOE and consequently have missing data at Week 6 are assumed to be representative of subjects that would not continue to use the drug outside of a clinical trial and their missing values following discontinuation will be imputed using MI based off the distribution of placebo values at the matching time point, conditioned on the observed data (including baseline) [redacted]. All other missing values (both intermittent and following study discontinuation) will be imputed using MI assuming that they are missing at random, conditioned on the observed data (including baseline) [redacted]. Sensitivity analyses will explore the results under different analysis assumptions.

Population-Level Summary

The population-level summary will be the difference in least-square means between treatment arms (analyzed as randomized) at Week 6 from the primary analysis model. See Section 8.2.2 for details.

5. STUDY SUBJECTS

5.1. Disposition of Subjects

The number and percentage of subjects in each analysis population will be summarized. The number of subjects screened, subjects enrolled, and the number and percentage of subjects completing treatment, discontinuing from treatment and reasons for treatment discontinuation will also be reported. Likewise, this will be repeated for study status: subjects completing the study, discontinuing from the study and reasons for study discontinuation will be reported. All percentages will be calculated using the number of subjects enrolled as the denominator.

All disposition data will also be provided in a data listing.

5.2. Demographic and Other Baseline Characteristics

Demographic and baseline characteristics such as age, gender, race/ethnicity, height, weight, body mass index (BMI), will be summarized by treatment group and overall for the ITT, mITT, PP, and Safety populations. Categorical items will be reported with counts and percentages; continuous items will be reported using summary statistics (mean, standard deviation [SD], median, minimum, maximum).

Additionally, the characteristics listed above will be presented in a data listing.

5.3. Prior and Concomitant Medications/Therapies

All medications taken within 3 months before screening, or any ADHD drug taken within 6 months before screening through study discontinuation, will be recorded in the electronic case report form (eCRF).

Prior treatments are defined as any treatment taken before study drug administration. Concomitant treatments are defined as treatments taken after the first dose of study drug. In the case of missing or partial dates, medications will be considered concomitant unless the available data excludes that possibility.

All medications will be coded using the World Health Organization Drug Dictionary (WHO-DD 2022-MAR, Global B3). Prior and concomitant medications will be summarized for the safety population by treatment group and by the number and percentage of subjects taking each medication, classified by using WHO-DD Anatomical Therapeutic Chemical (ATC) Level 3 and preferred term (PT).

All data related to prior and concomitant medications will also be presented in a data listing, with a flag included to indicate whether a medication was prior and/or concomitant.

Concomitant procedures will be presented in a listing.

5.4. Medical History

Medical History will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v25.0) and summarized for the safety population by system organ class (SOC) and PT using frequency counts and percentages by treatment group.

5.5. Substance Use

Data collected on substance use history will be provided in a data listing for all subjects in the Safety Population.

6. STUDY OPERATIONS

6.1. Protocol Deviations

Protocol deviations will be maintained on the study protocol deviation log. Protocol deviations will be collected and grouped into different categories, such as:

- Those who entered the study even though they did not satisfy the entry criteria.
- Those who met withdrawal criteria during the study but were not withdrawn.
- Those who received the wrong study drug, incorrect dose, or who had poor study drug compliance.
- Those who received an excluded concomitant treatment.

Protocol violations that impact efficacy evaluations will be determined by the principal investigator and sponsor prior to the unblinding of data and will lead to exclusion from the PP population.

Protocol deviations will be summarized by type, status as major or minor, and by treatment group for the Safety Population.

Individual protocol deviations will be listed by subject.

6.2. Randomization

This is a double-blind study. Unless otherwise specified, all study personnel are to remain blinded to study drug prior to database lock and final analysis following study unblinding.

Computer-generated randomization codes for each study arm will be assigned through Interactive Response Technology (IRT), with restrictions on the total number of subjects assigned to each group, thereby limiting imbalance in numbers between groups. Randomization will be stratified by site and LC cohort, to ensure approximately equal number of those on NRCT-101SR and placebo, and sex, to ensure approximately equal numbers of male and female subjects in NRCT-101SR and placebo groups. At randomization, the subject will automatically be assigned by IRT unique subject bottle numbers from the available stock on-site. The investigational product (IP) dispensation, accountability and destruction status will be maintained in the IRT system. The subject randomization status will also be maintained in the IRT system.

6.3. Measures of Treatment Compliance and Exposure

The treatment duration will be calculated and summarized for the safety population using summary statistics based on case report form (CRF) data for first and last dose dates (number of days = last dose date – first dose date + 1). If the date of last dosing is completely missing, then the date of last dosing will be taken for analysis purposes as the date the relevant study drug was last dispensed. If only the month of the last dose is recorded, the first day of the month will be assumed as the last dosing date.

Compliance is defined as taking at least 80% but not more than 120% of study drug between each clinic visit. Subjects will return all bottles and unused tablets at each clinic visit. The number of tablets taken divided by the number of tablets the subject should have taken in between visits multiplied by 100% will be used to calculate study drug compliance.

Compliance as a percentage will be summarized for the Safety Population with descriptive statistics by treatment arm. The number and percentages of subjects within certain categories of compliance (e.g., < 80%, 80% to ≤ 120%, > 120%) will also be presented.

A listing of drug accountability and study drug exposure data based on CRF data will be provided.

7. GENERAL ANAYLSIS AND REPORTING CONSIDERATIONS

7.1.1. Multicenter Studies

This is a multicenter study. Unless otherwise specified, data from all study sites will be pooled for all analyses.

For the purposes of modeling, a pooled variable may be utilized where sites with fewer than 5 subjects will be pooled into a single large site. If there are convergence issues, this will be repeated with a threshold of 10. If there are only 1-2 small sites that still result in insufficient counts when pooled, then they will be pooled with the next smallest site.

7.1.2. Assessment Time Windows

Subjects who withdraw/drop out from the study will have the early termination (ET) data collected at their ET visit included in the analysis at the closest visit where a given assessment should be collected per the schedule of assessments (Week 1, 3, 5, 6), using midpoints between visits to window the early termination. If this results in two records for a given visit, then the scheduled visit will be used, followed by the record closest to the targeted date.

7.1.3. Timing of Analyses

All final, planned analyses will be performed after the last subject has completed all study assessments, all relevant study data have been processed and integrated into the analysis database, and the database has been locked.

Any post-hoc, exploratory analyses completed to support planned study analysis, which were not identified in this SAP, will be documented, and reported in appendices to the CSR. Any results from these unplanned analyses (post-hoc) will also be clearly identified in the text of the CSR.

7.1.4. Multiple Comparisons/Multiplicity

The dual primary endpoints and key secondary efficacy endpoints will be tested with control for multiplicity. All tests will be two-sided. An alpha recycling approach will be utilized to maintain alpha = 0.05 and pass alpha to secondary endpoints.

1. The 0.05 alpha will be split equally and 0.025 allocated to each of the dual primary endpoints (change from Baseline to Week 6 in PERMP-C and in AISRS). The smaller p-value of the dual primary efficacy endpoints will be tested at the 0.025 level.
2. If the endpoint with the smaller p-value is not significant at 0.025, all testing will halt and all p-values will be declared non-significant.
3. If significant at 0.025, it will be declared successful and its 0.025 alpha passed to the second of the dual primary endpoints.
4. If the second of the dual primary endpoints is not significant at alpha = 0.05, it will be declared non-significant, all testing will halt and all subsequent p-values will be declared non-significant; success will only be declared on the stronger endpoint (step 3).

5. If the second of the dual primary endpoints is significant at alpha = 0.05, it will be declared significant and the remaining alpha = 0.05 passed to the key secondary endpoints.
6. If the first key secondary endpoint (BRIEF-A) is significant at alpha = 0.05, its 0.05 alpha will be passed to the second key secondary endpoint (HADS).
7. No additional adjustments for multiplicity will be applied to any of the other endpoints; p-values will be reported, but will be purely nominal.

7.1.5. Power and Sample Size

Sample size estimates for power = 85% were calculated using the following assumptions:

- 1:1 randomization ratio between placebo and NRCT-101SR
- Two-sample t test
- Two sided alpha = 2.5%
- Effect size = 0.5

Based on these, the total sample size for 85% power = 172. Due to the dual pimary outcomes and alpha control adjustment, an alpha of 0.025 is utilized and power is based on the above assumptions for PERMP; it is possible that the overall power, taking into account the additional primary of AISRS, is greater than 85%. To account for increased variaiblity due to dropout, a total of approximately 216 subjects (108 in each treatment group) are planned for 85% power.

8. ENDPOINT EVALUATION

8.1. Dual Primary Endpoint #1

The first primary efficacy endpoint is the change in PERMP-C from Baseline to Week 6 in those receiving NRCT-101SR compared to those receiving placebo. The primary analysis population will be the ITT population.

8.1.1. Computation of the Dual Primary Endpoint #1

PERMP is a timed (10-minute sessions) performance-based assessment for evaluating function in ADHD subjects. PERMP-C is the number of math problems answered correctly and typically ranges from 0 to 400, with higher scores indicating better performance. The PERMP total score (PERMP-T) is the sum of the number of math problems attempted (PERMP-A) and the number of math problems answered correctly (PERMP-C). The PERMP-T scores typically range from 0 to 800, with higher scores indicating better performance.

At each visit where collected (Baseline, Week 3, and Week 6), PERMP-C from six post-dose time points (2, 4, 6, 8, 10, and 12 hours) will be averaged across the time points to get the PERMP-C score for analysis. The change from Baseline in PERMP-C scores at the Week 3 and Week 6 visits will be calculated as this average across time points at a given visit minus the average across time points at baseline.

Missing data will be imputed as described in Section 8.3 below.

8.1.2. Primary Analysis of the Dual Primary Endpoint #1

Summary statistics (mean, SD, median, minimum, maximum) for the primary efficacy endpoint will be reported for the change from Baseline to Week 6 for each of the treatment groups. The primary efficacy endpoint will be analyzed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) with fixed effects for treatment group (NRCT-101SR and placebo), time (Week 3 and Week 6), the treatment-by-visit interaction; sex and baseline PERMP-C value will be included as a fixed covariates and site (possibly pooled) as a random effect. The outcome variables will be the PERMP-C change from baseline to each timepoint; the primary comparison will be the contrast between treatment groups at Week 6. An unstructured within-subject covariance matrix will be utilized along with Kenward-Rogers denominator degrees of freedom. Should this fail to converge under the standard Newton-Raphson algorithm, the Fisher scoring method will be attempted, followed by alternative methodology given in Lu, Mehrotra (Lu and Mehrotra 2010). In the unlikely event that none of these converge, the following structures will be attempted in order with the first to converge being selected: first-order ante dependence, heterogeneous first-order autoregressive, heterogeneous compound symmetry, and compound symmetry; sandwich estimator will be utilized for each.

Least squares (LS) means and differences across the 20 MI reps (see missing data imputation Section 8.3 below) will be combined using SAS procedure MIANALYZE (Rubin, 1976). Significance testing will be based on least-squares means and two-sided 95% confidence intervals (CIs) will be presented.

8.1.3. Sensitivity Analyses of the Dual Primary #1 Analysis

The following sensitivity analyses will be performed:

8.1.3.1. Multiple Imputation – Lost to Follow-up and "Other" as Missing Not at Random

The primary analysis will be repeated using the same MI approach, but subjects that drop out with loss to follow-up and "other" (unspecified) as the reason will be grouped with LOE and AE dropouts in the imputation algorithm.

8.1.3.2. Multiple Imputation – Baseline as reference distribution for Missing Not at Random

The primary analysis will be repeated using the same MI approach, but subjects that drop out for LOE and AE will be imputed using the distribution of the baseline values. This investigates an alternative hypothetical strategy where instead of assuming the values will revert to the distribution in the placebo group, all subjects (placebo and active) are assumed to revert to the distribution of baseline values.

8.1.3.3. Multiple Imputation Tipping Point

A tipping point analysis will be performed using the above MI datasets and applying an increasing penalty delta (PERMP-C) to the active group until statistical significance is no longer achieved. The delta will only be applied to imputed values; this will be done in 5-point increments on the PERMP-C score. This will only be performed if the primary analysis is significant. This will test the overall robustness of the primary analysis.

8.1.4. Secondary Analyses of the Dual Primary Endpoint #1

The following secondary and supporting analyses will be performed:

- PERMP-C will be analyzed at each visit comparing the within visit timepoints using the change from baseline to each time-matched value. These will be analyzed using a REML-based MMRM with fixed effects for treatment group (NRCT-101SR and placebo), time point, the treatment-by-time point interaction; sex and baseline PERMP-C value will be included as a fixed covariate and site (possibly pooled) as a random effect. An unstructured within-subject covariance matrix will be utilized along with Kenward-Rogers denominator degrees of freedom. Failure to converge will be handled as described in the primary analysis.

  Model results will be presented graphically with the LS means and 95% CIs from the model above plotted for each time point and treatment for Week 3 and Week 6 separately.

- In addition to the change from baseline to Week 6 in the PERMP-C score, the change from baseline at Week 3 will also be reported out of the primary MMRM model described in Section 8.1.2.

- The primary analysis will be repeated on the mITT and PP populations.

- The primary analysis will be repeated including additional covariates as main effect and interactions with treatment in the primary analysis model. The LS means treatment difference, its 95% CI and p-value within each subgroup will be reported from the model. [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

8.2. Dual Primary Endpoint #2

The second primary efficacy endpoint is the change in AISRS from Baseline to Week 6 in those receiving NRCT-101SR compared to those receiving placebo. The primary analysis population will be the ITT population.

8.2.1. Computation of the Dual Primary Endpoint #2

The AISRS is collected at baseline, Week 1, Week 3, and Week 6; at each visit, the change from baseline will be calculated as the score at the visit minus the baseline score. Because it is only collected once at each visit, no averaging across time points as described for the PERMP-C will be required.

Missing data will be imputed as described in Section 8.3 below.

8.2.2. Primary Analysis of the Dual Primary Endpoint #2

Summary statistics (mean, SD, median, minimum, maximum) for the primary efficacy endpoint will be reported for the change from Baseline to Week 6 for each of the treatment groups. The primary efficacy endpoint will be analyzed using a REML-based MMRM with fixed effects for treatment group (NRCT-101SR and placebo), time (Week 1, Week 3, and Week 6), the treatment-by-visit interaction; sex and baseline AISRS value will be included as a fixed covariate and site (possibly pooled) as a random effect. The outcome variables will be the AISRS change from baseline to each timepoint; the primary comparison will be the contrast between treatment groups at Week 6. An unstructured within-subject covariance matrix will be utilized along with Kenward-Rogers denominator degrees of freedom. Should this fail to converge under the standard Newton-Raphson algorithm, the Fisher scoring method will be attempted, followed by alternative methodology given in Lu, Mehrotra (Lu and Mehrotra 2010). In the unlikely event that none of these converge, the following structures will be attempted in order with the first to converge being selected: first-order ante dependence, heterogeneous first-order autoregressive, heterogeneous compound symmetry, and compound symmetry; sandwich estimator will be utilized for each.

LS means and differences across the 20 MI reps (see missing data imputation in Section 8.3 below) will be combined using SAS procedure MIANALYZE (Rubin, 1976). Significance testing will be based on LS means and two-sided 95% CIs will be presented.

8.2.3. Sensitivity Analyses of the Dual Primary #2 Analysis

The following sensitivity analyses will be performed:

8.2.3.1. Multiple Imputation – Lost to Follow-up and "Other" as Missing Not at Random

The primary analysis will be repeated using the same MI approach, but subjects that drop out with loss to follow-up and "other" (unspecified) as the reason will be grouped with LOE and AE dropouts in the imputation algorithm.

8.2.3.2. Multiple Imputation – Baseline as reference distribution for Missing Not at Random

The primary analysis will be repeated using the same MI approach, but subjects that drop out for LOE and AE will be imputed using the distribution of the baseline values. This investigates an alternative hypothetical strategy where instead of assuming the values will revert to the distribution in the placebo group, all subjects (placebo and active) are assumed to revert to the distribution of baseline values.

8.2.3.3. Multiple Imputation Tipping Point

A tipping point analysis will be performed using the above MI datasets and applying an increasing penalty delta AISRS to the active group, until statistical significance is no longer achieved. The delta will only be applied to imputed values; this will be done in 1-point increments on the AISRS score. This will only be performed if the primary analysis is significant. This will test the overall robustness of the primary analysis.

8.2.4. Secondary Analyses of the Dual Primary Endpoint #2

The following secondary and supporting analyses will be performed:

- In addition to the change from baseline to Week 6 in the AISRS score, the change from baseline at Week 1 and Week 3 will also be reported out of the primary MMRM model described in Section 8.2.2.
- The primary analysis of AISRS will be repeated on the mITT and PP populations.
- The primary analysis will be repeated including additional covariates as main effect and interactions with treatment in the primary analysis model. The LS means treatment difference, it's 95% CI and p-value within each subgroup will be reported from the model. [redacted]
  - [redacted]
  - [redacted]

- [redacted]
- [redacted]
- [redacted]

8.3. Missing Data Imputation

Missing data will be imputed for the dual primary endpoints as well as the key secondary endpoints.

For PERMP endpoints taken at multiple time points within a visit, the visit value will be the average of the values for that visit, as long as at least three post-dose assessments are performed; missing values within a visit will be assumed to be missing at random.

Missing values for subjects in the ITT population will be imputed via MI. When the study medication is discontinued due to LOE or due to an AE, missing values will be imputed drawing from the placebo distribution at the matching time points, conditioned on the observed data under the assumption that they are missing not at random (MNAR), with a covariate for sex. If the study medication was discontinued for any other reason (including impacts from the COVID-19 pandemic), values will be imputed within treatment group using MI, under the assumption that they are missing at random (MAR), with covariates sex and observed values recorded at each time point. For the purposes of the imputation algorithm, AE discontinuations due solely to COVID and COVID sequelae will be included in the MAR imputation grouping. Subjects that withdraw due to COVID and have an independent, unrelated AE that also results in study discontinuation will be included in the MNAR imputation grouping (with all other AE withdrawals other than the aforementioned COVID exclusion). The MAR approach will also be applied for sporadic missing values (prior to discontinuation). The MI process will use 20 repeats in the analysis datasets generated.

The steps will be as follows:

1. Intermittent missing values for both completers and dropouts prior to discontinuation will be imputed using the Markov Chain Monte Carlo (MCMC) method implemented with the SAS MI procedure.
2. For subjects that do not discontinue for LOE or AEs, a MAR imputation will be applied: the monotone missing values will be imputed with the SAS MI procedure using the monotone regression method. Baseline and the post-baseline scores at each visit will be included as covariates as well as sex; imputation will be done within treatment group. This will also apply for subjects that complete, but have their final value missing.
3. For subjects that discontinue for LOE or AEs, values will be imputed using the placebo group as reference. Missing values will be imputed with the SAS MI procedure using the monotone regression method. Baseline and the post-baseline scores at each visit will be included as covariates [redacted].

Subjects that discontinue study drug or early terminate from the study but provide data will have all observed data used.

8.4. Secondary Endpoints

All secondary efficacy analyses will be based on the ITT population.

8.4.1. Key Secondary Endpoints

There will be two key secondary endpoints:

8.4.1.1. Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A)

The BRIEF-A will be collected at Baseline, Week 1, Week 3, and Week 6. Summary statistics (mean, SD, median, minimum, maximum) will be reported for the values and the changes from Baseline to Week 6 for each of the treatment groups.

The change from baseline will be modeled in an MMRM identical to that described for the dual primary endpoints. No imputation will be performed; however, the MMRM model will return unbiased estimates under the assumption that data are missing at random.

LS means, standard errors, and 95% CIs will be reported for each treatment and visit as well as the difference between treatments at each visit. The primary visit of interest is Week 6.

8.4.1.2. Hospital Anxiety and Depression Scale (HADS)

The HADS will be collected at Baseline, Week 1, Week 3, and Week 6. For each domain (anxiety and depression), summary statistics (mean, SD, median, minimum, maximum) will be reported for the values and the change from Baseline to Week 6 for each of the treatment groups.

The change from baseline for each domain will be modeled in an MMRM identical to that described for the dual primary endpoints. No imputation will be performed; however, the MMRM model will return unbiased estimates under the assumption that data are missing at random.

LS means, standard errors, and 95% CIs will be reported for each treatment and visit, as well as the difference between treatments at each visit. The primary visit of interest is Week 6.

8.4.2. Additional Secondary Endpoints and Other Endpoints

8.4.2.1. Continuous Secondary Endpoints

Each of the following continuous endpoints will be summarized:

- Change from Baseline in the Clinical Global Impression – Severity (CGI-S)
- Change from Baseline in the Adult ADHD Quality of Life scale (AAQoL)
- Change from Baseline in the AISRS Expanded Version
- Change from Baseline in the Work Productivity and Activity Impairment questionnaire (WPAI)

For each of the above, summary statistics (mean, SD, median, minimum, maximum) for the primary efficacy endpoint will be reported for the change from the Baseline to Week 6 for each

of the treatment groups. Each will be analyzed using a REML-based MMRM with fixed effects for treatment group (NRCT-101SR and placebo), time (Week 1, Week 3, and Week 6), the treatment-by-visit interaction, site (possibly using pooled sites), and sex. Baseline value for each endpoint will be included as a covariate. The outcome variables will be the change from baseline to each timepoint; the primary comparison will be the contrast between treatment groups at Week 6. An unstructured within-subject covariance matrix will be utilized along with Kenward-Rogers denominator degrees of freedom. Should this fail to converge under the standard Newton-Raphson algorithm, the Fisher scoring method will be attempted, followed by alternative methodology given in Lu, Mehrotra (Lu and Mehrotra 2010). In the unlikely event that none of these converge, the following structures will be attempted in order with the first to converge being selected: first-order ante dependence, heterogeneous first-order autoregressive, heterogeneous compound symmetry, and compound symmetry; sandwich estimator will be utilized for each.

8.4.2.2. Categorical Secondary Endpoints

The following categorical endpoints will be tabulated:

- [redacted]
- [redacted] ≥ 2[redacted]
- Proportion of subjects that are composite responders (≥ 25% reduction of AISRS and ≥ 2-point reduction of CGI-S from Baseline to Week 6)

The number and percentage of responders (with response for each as described above) and non-responders will be reported, with missing values considered non-responders. 95% CIs of the percentages will be given, as well as the difference between treatment groups in percentages, its 95% Wald CI, and p-value comparing the groups. Groups will be tested using a difference in proportions Z test (equivalent to a Pearson's Chi-Squared). In the case of low cell counts (< 5 expected in a given cell), then Fisher's exact test will be used instead.

8.4.2.3. Other Endpoints

Each of the following continuous endpoints will be summarized:

- [redacted]
- [redacted]
- [redacted] – [redacted] – [redacted]

For each of the above, summary statistics (mean, SD, median, minimum, maximum) will be reported for the change from baseline to Week 6 for each of the treatment groups. The change from baseline will be analyzed using a MMRM, similar to the primary efficacy endpoint. For all endpoints, the time point of primary interest is Week 6.

9. SAFETY EVALUATION

9.1. Overview of Safety Analysis Methods

All safety analyses will be completed for the Safety Population. All safety data will be tabulated and listed. No formal statistics or imputation will be performed for the safety analysis. Safety and tolerability will be assessed by:

- Incidence of AEs and serious adverse events (SAEs) throughout the entire duration of the study
- Changes from baseline in electrocardiogram (ECG) results
- Changes from baseline in clinical laboratory test results
- Changes from baseline in vital signs
- Indications of increased suicidal ideation or behavior as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS)

9.2. Adverse Events

All AEs will be coded using MedDRA version 25.0.

A treatment-emergent AE (TEAE) is defined as any AE that has an onset on or after the dose of study drug, or any pre-existing condition that has worsened on or after the first dose of study drug.

An AE summary table will present totals for the following:

- All TEAEs
- TEAEs by severity (mild, moderate, severe, life threatening, death)
- TEAEs leading to study discontinuation
- TEAEs by relationship (unrelated, related, see below)
- SAEs

The incidence of TEAEs (number and percentage of subjects reporting the AE at least once during the study), SAEs and TEAEs related to study drug will be summarized by treatment.

The incidence of TEAEs and study drug administration-related TEAEs will also be summarized by maximum severity and most-related relationship to study drug by MedDRA primary SOC and PT. The summary will include the total number and percentage of subjects reporting an event. An AE is said to be study drug administration-related if it is marked as ‘possibly related’, ‘probably related’ or ‘definitely related’ on the CRF.

In recording events, a continuous event, i.e., reported more than once and which did not cease, will be counted only once; non-continuous AEs reported several times by the same subjects will be recorded as multiple events. However, for reporting, each subject will be counted only once within each summation level (SOC and PT). If a subject experiences more than one TEAE within each summation level, the TEAE with the strongest relationship or the maximum severity, as appropriate, will be included in the summaries by relationship and severity.

All AEs will be presented in a listing.

These summaries will include SAEs; additionally, they will be presented separately (see below).

9.3. Deaths, Serious Adverse Events, and Other Significant Adverse Events

Summaries of incidence rates (frequencies and percentages) of individual SAEs by MedDRA SOC and PT will be presented, as well as SAEs related to study drug. Additionally, SAEs will be listed separately.

TEAEs leading to discontinuation of study will be analyzed and presented in a manner identical to the SAEs.

All deaths will be reported in a listing.

9.4. Clinical Laboratory Evaluation

Mean changes from baseline at each post-baseline time point for each numeric laboratory variable will be presented. In addition, each reading will be classified as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift from baseline tables for the follow-up measurements will be presented.

Laboratory values will be displayed in the data listings with their corresponding normal ranges, and those values that are outside the normal range will be flagged.

Results of urine drug screens and pregnancy tests will be presented in listings.

[redacted]

9.5. Vital Signs, ECGs, Physical Findings, and Other Observations Related to Safety

9.5.1. Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline at each assessment time point will be reported for vital signs including weight (kg), BMI (kg/m^2), body temperature (°F), heart rate (beats/min), respiratory rate (breaths/min), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg). Vital sign values, including abnormal values, will be listed.

9.5.2. ECGs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline at each assessment time point will be reported for the following ECG parameters:

- Heart Rate (beats/min)
- PR Interval (msec)
- QT Interval (msec)
- QTcF (msec)
- QRS Duration (msec)
- RR Interval (msec)

The ECG interpretation will be in the CRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. The number and percentage of subjects in each category will be reported at each visit. The ECG cardiac rhythm will be collected in the CRF as regular or irregular. The number and percentage of subjects in each category will be reported at each visit.

ECG values, including interpretation and cardiac rhythm, will be listed.

9.5.3. Physical Examinations

Physical examination data will be presented in a data listing.

9.5.4. Columbia Suicide Severity Rating Scale (C-SSRS)

C-SSRS findings at all visits will be presented in a listing for any subject with emergent increase in ideation or any suicidal behavior.

9.5.5. Pregnancy Reporting

Any data relating to pregnancies reported during the study will be provided in a data listing.

10. OTHER ANALYSES

10.1. Exploratory Analyses

Additional subgroups may be investigated using the primary analysis approach for each endpoint, performed within the given subgroup. These analyses are purely exploratory and may not be performed if insufficient subjects are available in a subgroup of interest.

Exploratory covariate analyses may be performed for endpoints in addition to the dual primary endpoints.

10.2. PK Analysis

At Week 3, PK sampling will be completed pre-dose, 4- and 7-hours post-dose with a 30-minute window for completion of sampling. Descriptive statistics will be reported for the concentrations for each analyte and each timepoint for the subjects in the active group. In addition to the standard descriptive statistics, geometric means and geometric SDs will be reported. Individual subjects may be excluded from these analyses in the case that they accidentally dose prior to the visit. Likewise, individual time point values may be excluded if they are biologically implausible.

Mean concentration curves will be displayed graphically on both the natural and log scale.

11. INTERIM ANALYSES

No interim analyses are planned.

12. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

The protocol stated that clinically significant vital sign changes would be summarized; clinical significance was not collected for vital signs.

The primary models included site as a fixed effect; this has been updated to be a random effect and details on site pooling (if necessary) have been added.

Additional details of the sensitivity and covariate analyses have been added.

13. REFERENCES

ICH Topic E3 Structure and Content of Clinical Study Reports. July 1996.

ICH Topic E9 Statistical Principles for Clinical Trials. September 1998.

Lu K. and Mehrotra D.V. Specification of covariance structure in longitudinal data analysis for randomized clinical trials. Statistics in Medicine 2010 Feb 20; 29(4):474-88.

Rubin, D. B. (1976), “Inference and Missing Data”, Biometrika, 63, 581–592.

14. APPENDIX

14.1. Schedule of Events

Schedule of Events	Screening	LC Orientation	Baseline (LC)	Week 1 (clinic)	Week 3 (LC)	Weeks 5 (remote)	Week 6 or ET (LC)	Week 7 Follow-up (remote)
Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Day	Day -42 to -2	Day -8 to -1	Day 1	Day 8 (+/- 1 day)	Day 22	Day 36 (+/-3 days)	Day 43	Day 50 (+/-2 day)
Informed Consent	X							
Eligibility Review	X		X					
Randomization			X					
Demographics & Medical History	X							
Substance Abuse History	X							
Prior/ Concomitant Meds	X	X	X	X	X	X	X	X
Physical Exam	X		X		X		X	
MINI with DSM-5 probes	X							
Vital Signs including weight	X	X	X		X		X	
Height	X							
Safety Labs/Urinalysis	X		X[f]		X		X	
Urine pregnancy	X		X					
Urine Drug Screen	X		X		X		X	
[redacted]			X				X	
ECG			X				X	
PK Sampling[a]					X			
AISRS with expanded version	X		X[g]	X[g]	X[g]		X[g]	
[redacted]			X		X		X	
CGI-S	X		X	X	X		X	
[redacted]			X		X		X	
AAQoL			X		X		X	
BRIEF-A			X	X	X		X	

Schedule of Events	Screening	LC Orientation	Baseline (LC)	Week 1 (clinic)	Week 3 (LC)	Weeks 5 (remote)	Week 6 or ET (LC)	Week 7 Follow-up (remote)
Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Day	Day -42 to -2	Day -8 to -1	Day 1	Day 8 (+/- 1 day)	Day 22	Day 36 (+/-3 days)	Day 43	Day 50 (+/-2 day)
HADS			X	X	X		X	
C-SSRS (Baseline/Screening version)	X							
C-SSRS (since last visit version)		X	X	X	X	X	X	X
[redacted]			X		X		X	
PERMP placement	X							
PERMP practice[c]	X	X						
PERMP			X[bg]		X[bg]		X[bdg]	
Adverse Events				X	X	X	X	X
Study Drug Dispensation			X		X		X[e]	
Study Drug Accountability					X		X	

ET = early termination; LC = Laboratory Classroom; AISRS = ADHD Investigator Symptom Rating Scale; ECG = electrocardiogram; [redacted]; CGI-S = Clinician Global Impression - Severity; [redacted]; AAQoL = adult ADHD Quality of Life; BRIEF-A = Behavior Rating Inventory of Executive Function – Adult; HADS = Hospital Anxiety and Depression Scale; C-SSRS = Columbia Suicide Severity Rating Scale; PERMP = Permanent Product Measure of Performance; PK = Pharmacokinetic (samples collected pre-dose and post-dose); [redacted]; RBC = red blood cells

[a] PK sampling will be completed pre-dose, 4- and 7-hours post-dose with a 30-minute window for completion of sampling.
[b] PERMP is administered 7 times at LC visits.
[c] PERMP practice is administered 3 times at screening visit (Visit 1) and 5 times at orientation visit (Visit 2).
[d] PERMP is not administered at ET visit if subject has discontinued study drug.
[e] Final study drug doses are taken in clinic at Visit 7 as per the LC schedule (refer to LC manual).
[f] Baseline safety labs including urinalysis do not need to be collected if screening visit results are within 30 days of the Baseline visit. However, samples may still be collected to confirm subject eligibility as needed.
[g] Placebo Control Reminder Script (PCRS) should be administered once per visit prior to conducting any of these assessments.

14.2. Random Seeds

The following list of numbers will be used for random seeds where required for MI processes:

4735132

5857952

5213956

5927162

4195486

4222382

3418814

2867763

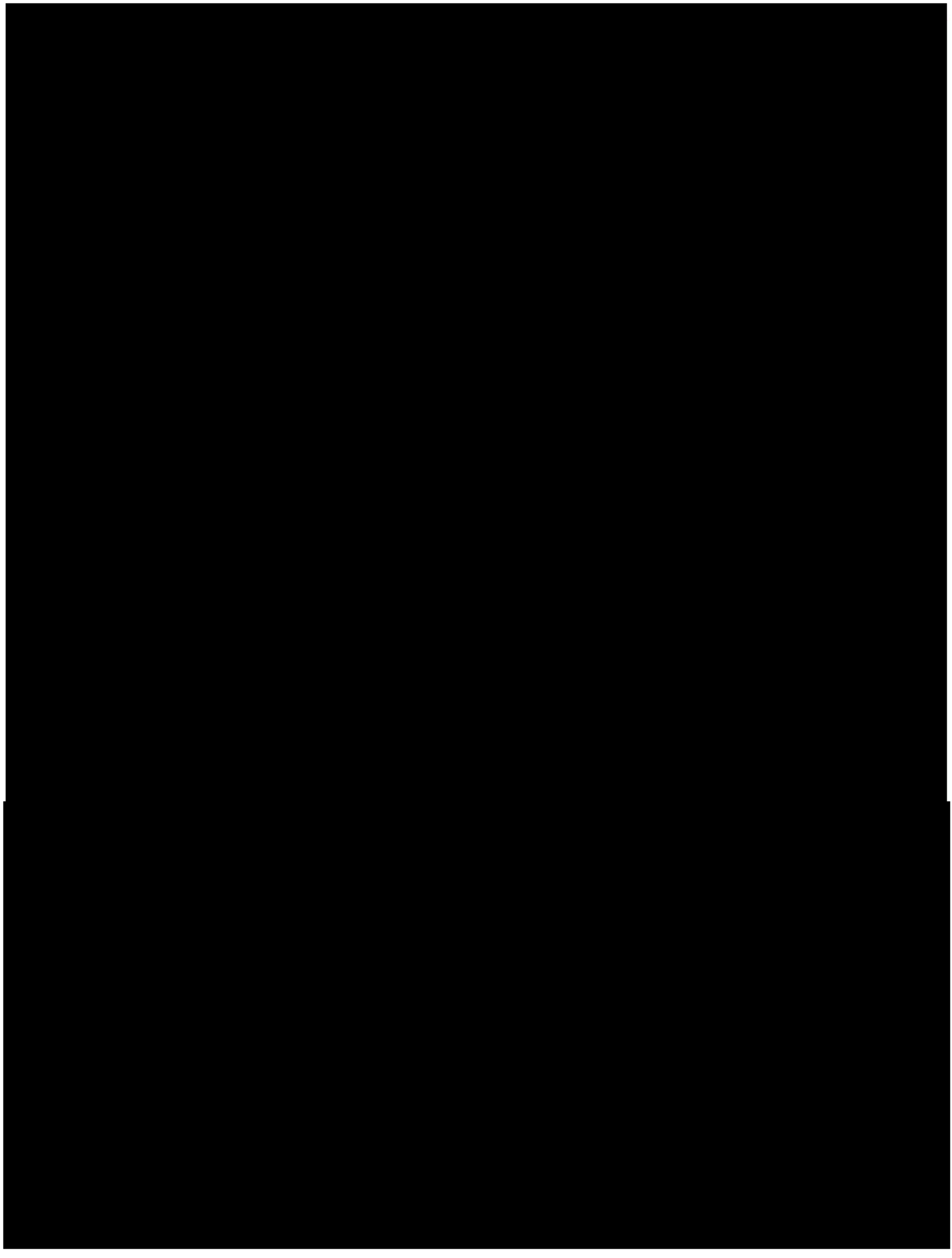
8995736

5775152

These will generally be used in order for the primary analysis, then secondary endpoints and sensitivity analyses. For cases where identical code may be applied to more than one outcome or a sensitivity analysis that uses a minor variation on the primary code, the second to last digit will be incremented by 1 to produce new seeds for the subsequent outcome/analysis. If a single dataset requires more than the 10 seeds above, additional seeds will be generated by incrementing the last digit by 1. All seeds used will be documented in the programming specifications and the programs themselves.

15. ATTACHMENTS

N/A



[redacted]

[redacted]