Selective serotonin reuptake inhibitor add-on to stimulant medication in youth with severe mood dysregulation

A double-blind randomized controlled trial of adjunctive citalopram in youth with chronic severe irritability treated with stimulant

Statistical Analysis Plan

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Quantitative Analysis Plan

This document details the presentation and analysis strategy for the primary paper reporting results from this trial. It is intended that the results reported in this paper will follow the strategy set out herein; subsequent papers of a more exploratory nature will not be bound by this analysis plan but will be expected to follow the broad principles laid down for the principle paper(s). The principles are not intended to curtail exploratory analysis or to prohibit sensible statistical and reporting practices but they are intended to establish the strategy that will be followed as closely as possible, when analyzing and reporting the trial. Reference was made to the trial protocol version 12, ICH guidelines on Statistical Principles (ICH E9 (1998)) reference and CONSORT guidelines {Moher, 2010 #4089}.

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1.1. Brief description of the trial

Severe mood dysregulation (SMD) is a common syndrome in children and adolescents, characterized by very severe irritability - including persistent anger and frequent outbursts - as well as distractibility, hyperactivity, and other symptoms of attention deficit hyperactivity disorder (ADHD).

Many children with SMD receive the diagnosis of bipolar disorder (BD) in the community, although they do not have clear manic episodes (with symptoms such as extreme happiness and decreased need for sleep). However, today we know that SMD and BD differ in family history of psychiatric disorders, pathophysiological mechanisms and longitudinal outcomes. For example, SMD presents high comorbidity with anxiety disorders and is associated with anxiety and depression in longitudinal studies, but not with BD. Furthermore, we know that lithium, a medication typically used to treat BD, does not improve irritability in youth with SMD. To date, there are no randomized trials that have examined pharmacological treatments for SMD with irritability as primary outcome.

ADHD is primarily treated with stimulant medication; and the first pharmacological option for anxiety and depression are selective serotonin reuptake inhibitors (SSRI). Given the presence of ADHD symptoms in SMD, and the specific association with anxiety and depression, this study will evaluate the effectiveness of the stimulant medication methylphenidate when combined (or not combined) with the SSRI citalopram, in treating symptoms of SMD in children and adolescents.

1.1.1. Principal research objectives to be addressed

The hypothesis is that we will demonstrate that citalopram added to methylphenidate improves irritability symptoms to a greater extent than placebo added to methylphenidate.

Primary objectives

To conduct a Phase II RCT to test the efficacy of citalopram plus methylphenidate vs. placebo plus methylphenidate in decreasing irritability in youth with severe mood dysregulation.

Secondary objectives

To assess the effects of citalopram + methylphenidate on several secondary measures, such as depressive symptoms, anxiety symptoms, side effects, and overall functional impairment.

1.1.2. Trial design

The trial is designed as a double-blind two-arm parallel groups randomized control trial. Children and adolescents aged 7-17 years old will be randomized to either a citalopram plus methylphenidate arm or a placebo plus methylphenidate arm.

Specifically, the trial is comprised of four mandatory phases and one optional phase. During Phase I participants will withdraw of their current medication (duration flexible, depending on the patient's medication at admission). Phase II consists of a medication free

period (one week). Phase III involves open treatment with methylphenidate to find the optimal dose (up to 5 weeks). Phase IV is the treatment phase, in which the randomized trial of citalopram plus methylphenidate vs. placebo plus methylphenidate is undertaken (8 weeks). After Phase IV, blindness will be broken. Finally, an optional Phase V will include open treatment as indicated in preparation for return to community care (**Figures 1 and 2**). Medication withdrawal, the medication-free week, the methylphenidate open trial, and initial dose stabilization using citalopram/placebo will occur while patients are either hospitalized or attending the Day Treatment Center. During the 8-week citalopram/placebo trial and subsequent open treatment, patients can be hospitalized, in day treatment, or outpatients, according to what is clinically appropriate (**Figure 1**). Participants will be assessed in the clinic weekly. Baseline measures will be collected just after admission into the protocol, prior Phase I (Baseline 1), before starting the open trial with methylphenidate at Phase III (Baseline 2) and just after randomization in Phase IV (Baseline 3). Outcomes will be based on change in reference to Baseline 1 and Baseline 3.

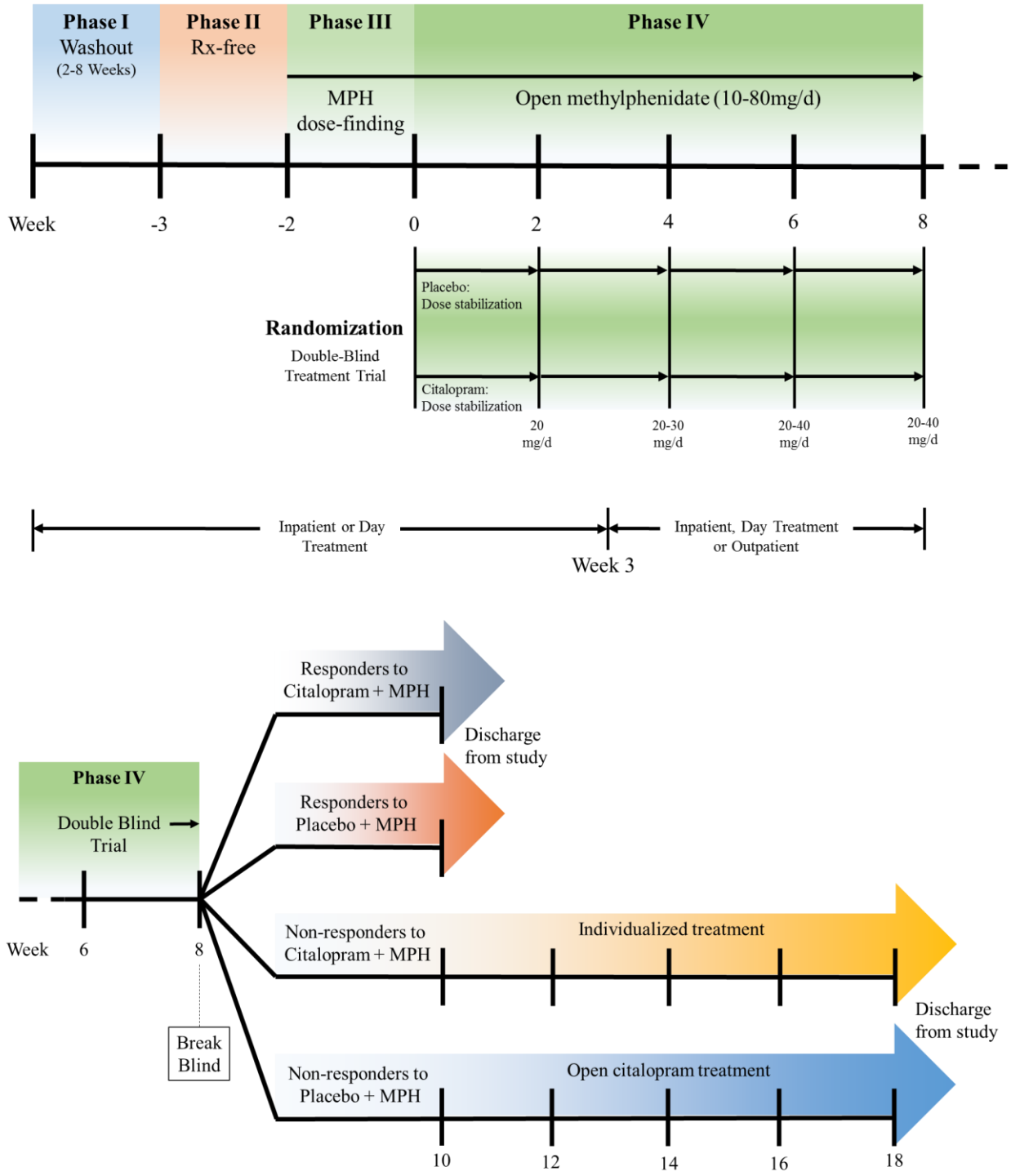

Figure 1. Trial design diagram

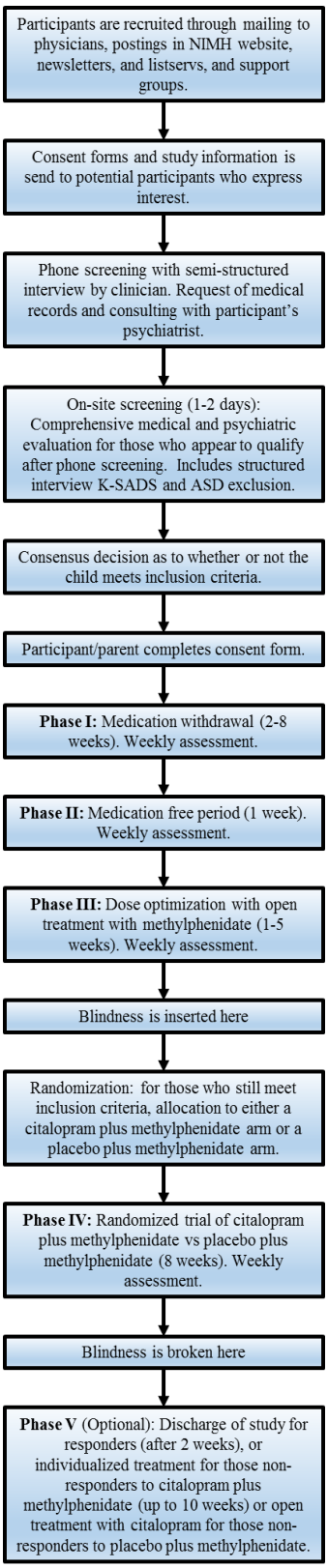

Figure 2. Trial design flow diagram

1.1.3. Method of allocation of groups

The study was randomized by the Pharmaceutical Development Service of the National Institutes of Health Clinical Center Pharmacy Department using a random numbers table. It was randomized in alternating blocks of six and four in a 1:1 ratio.

Participants and their parents will be blind to treatment allocation. The patient's research physician, primary NIMH clinician who performs mood ratings, and nursing staff will also be blind to treatment allocation.

1.1.4. Duration of the treatment period

The duration of the study (exclusive of open treatment at the end) is approximately 12-15 weeks, depending on the time required for medication discontinuation. As mentioned in section 1.1.2 of this document, the active intervention (Phase IV) consists of 8 weeks.

1.1.5. Frequency and duration of follow-up

Participants will be assessed in the clinic once a week beginning at the medication withdrawal period (Phase I) until the end of the randomized trial period (Phase IV). There are no follow-up assessments.

1.1.6. Visit windows

The first assessment will take place before the medication withdrawn period (Baseline 1). The final assessment will take place after the randomized trial (Week 8 of Phase IV). Assessments between the first and final collection of measures will be done once a week.

Typically, there was a 2 day visit window (for the inpatients, most were done the same day every week) but it might shift slightly for outpatients—except for end of week 8 which was exact.

1.1.7. Eligibility screening

Potential SMD participants will be screened via phone. Those who seem to meet inclusion criteria will be seen and screened in person in the clinic. If criteria are met, after this point, participants must give written consent to participate in the trial. After withdrawn medication period, free medication period, and open trial with methylphenidate, participants are rescreened for inclusion criteria prior to randomization. Inclusion and exclusion criteria are described in section III.A and III.B of the protocol, respectively.

1.1.8. Measures

The mechanisms for which all of the following measures will be recorded are described in detail in the protocol in section IV.

Baseline

The following demographics will be measured at baseline for the child participant:

- Ethnicity (White; Asian; Black or African American; Mixed; Unknown)
- Age (years)
- Sex
- Religion (Anglicanism; Baptist; Catholicism; Christian; Greek Orthodox; Judaism; Protestantism; Non-Denominational; None; Unknown)

The following measure will be collected during the first on-site screening to evaluate inclusion/exclusion criteria:

- Child Schedule for Affective Disorders Present and Lifetime Version (K-SADS-PL) with an additional supplement for SMD {Kaufman, 1997 #2116}.
- Autism Screening Questionnaire {Berument, 1999 #4077;Berument, 1999 #4077}, the Social Responsiveness Scale (SRS) {Constantino, 2003 #4078}, and the Children's Communication Checklist {Bishop, 1998 #4079}, so that children with probable PDD can be identified and, if symptoms are severe, excluded from the protocol.
- Full-scale intelligence quotient (FSIQ) was measured by the Wechsler Abbreviated Scale of Intelligence (WASI) {Wechsler, 1999 #2479}.

Outcome measures

All outcomes measures will be first collected before the medication withdrawn period (Baseline 1) and then every other week during this period, and the free medication period. The same measures will be collected before the open treatment with methylphenidate (Baseline 2) and then every other week until before randomization for the trial. Then, the same measures will be collected just after randomization (Baseline 3) and then every other week (8 weeks total) until the end of the trial.

Primary outcome measures

Our primary outcome measure will be the Clinical Global Impressions (CGI) for Irritability {Spearing, 1997 #4087}. Specifically, we will measure current severity of irritability (CGI-S) and improvement or change in relation to baseline (CGI-I), both baseline 1 and baseline 3.

The CGI is rated on a 7-point scale, with the severity of illness scale (CGI-S) using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients). CGI-I scores range from 1 (very much improved) through to 7 (very much worse).

Trial response will be defined as a CGI-I score less than 3 at the trial's end (i.e., children who received scores of 2 [much improved], or 1 [symptom free]).

Secondary outcome measures

Several secondary outcomes will be used to assess secondary objectives, as mentioned in section 1.1.1. Namely, to assess the side effects and adverse events of prescribed medications, as well as depressive symptoms, anxiety symptoms and global functional impairment:

- Side Effects will be measured with Dosage Record & Treatment Emergent Symptom Scale (DOTES) {Garvey, 1991 #4088}.
- Depressive symptoms will be measured with the Children's Depression Rating Scale (CDRS) {Poznanski, 1996 #3011}.
- Anxiety symptoms will be measured with the Pediatric Anxiety Rating Scale (PARS) {Riddle, 2002 #3010}.
- Global functional impairment will be measured with the Children's Global Assessment Scale (CGAS) {Shaffer, 1983 #2478}.

1.1.9. Sample size estimation (including clinical significance)

The calculation for the protocol assumed a response rate of 60% to citalopram+MPH and 20% to placebo+MPH. While, on the surface, this might seem like a somewhat large clinical difference, when SSRIs are highly effective in pediatric conditions, such as pediatric anxiety disorders, effect sizes of this magnitude are typically found {Ipser, 2009 #4086}.

Since there are no treatment trials in SMD targeting irritability, the placebo response rate is based on the MTA, a large treatment trial in ADHD using stimulants {Galanter, 2003 #4084;Greenhill, 2001 #4085}. Assuming power=0.8 and a two-tailed alpha= 0.05, a sample size of 56 (28 in each group) is needed. However, of course, in the event that the response to SSRIs in SMD is more similar to that in pediatric MDD than pediatric anxiety, power will be less than 0.8 {Wagner, 2004 #4082;Cipriani, 2016 #4083}.

Our experience with a previous treatment trial in this population suggests that roughly 50% of participants might not reach the point of randomization because of behavioral improvement, withdrawal from the study because of homesickness, or intolerance of medication discontinuation. Thus we are anticipating enrolling 112 children in order to ascertain 80 who will be randomized.

1.1.10.Brief description of proposed analyses

Analyses will be carried out by the trial statistician (PVR), following this SAP, and blind to treatment arm, once the database has been locked. Data will be analyzed with an intention-to-treat approach (i.e. analyze all those with data in groups as randomized irrespective of treatment received).

There will be descriptive statistics reported on the measures mentioned in 1.1.8, with an aim to comparing the treatment arms, and to review the patient demographics.

For the primary analysis, to test efficacy of citalopram plus methylphenidate vs. placebo plus methylphenidate in decreasing irritability in youth with SMD, a multilevel mixed-effects growth curve regression will be fitted for all continuous measures.

Further details of the analyses are given later on in this document.

Data summaries and analyses will be carried out in Stata 14.0.

1.2. Data Analysis Plan - Data Description

1.2.1. Recruitment, eligibility and representativeness of patients

A CONSORT flow chart will be constructed – see **Figure 3**. The number of patients will be summarized using the following categories: total number of patients contacted; eligible; consenting; and randomized.

Then by treatment arm: patients compliant and non-compliant with intervention; continuing through the trial; withdrawing; and excluded or analyzed.

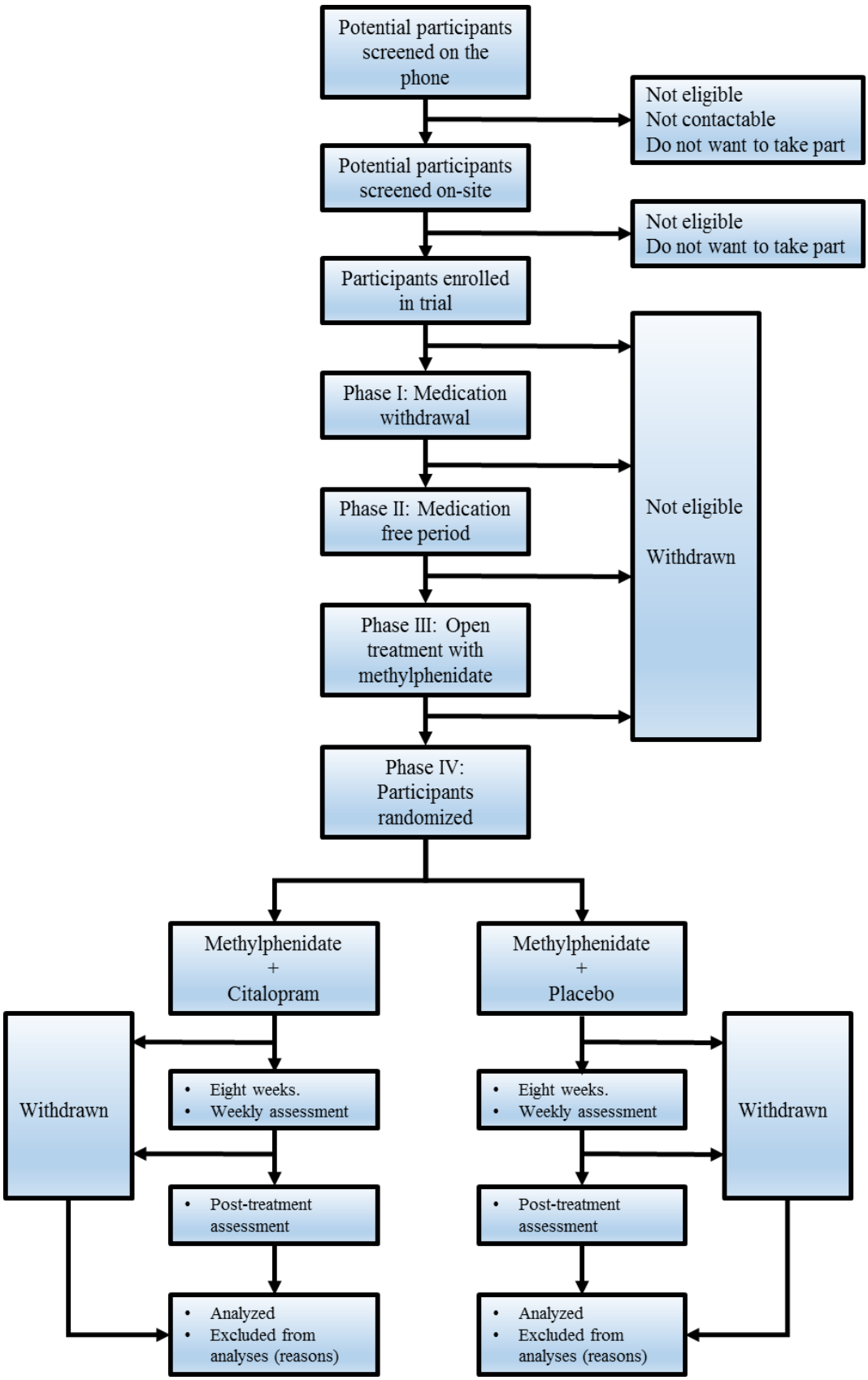

Figure 3. CONSORT Diagram

1.2.2. Baseline comparability of randomized groups

Table 1 will present, for all available cases, means and standard deviations (proportions and frequencies for categorical variables) disaggregated by treatment group for baseline values of variables contributing to the primary and secondary outcomes and background participant socio-demographic variables. No statistical significance tests or confidence interval will be calculated for the difference between randomized groups on any participant level baseline variables. The randomisation of intervention groups to participants should have ensured that any imbalance over all measured and unmeasured baseline characteristics is due to chance {Altman, 1991 #4080}.

1.2.3. Adherence to allocated treatment

Any departures from intended treatment assignment will be described by the number of weeks completed. Adherence to allocated treatment will be defined as being adhered minimum 6 weeks out of 8 weeks (i.e., minimum 75%)(~~minimum 6~~).

1.2.4. Loss of cases and other missing data

Table 1 will also present the numbers with endpoint data within each randomized group for each outcome. The major known reasons for loss to follow-up will be described and any systematic differences by treatment group in the characteristics of those lost will be described.

1.2.5. Assessing quality of outcome measures

Treatment blind analysis will be carried out to assess quality of data collected, checking that measures conform to appropriate ranges, that scatter plots show no implausible patterns, and dates conform to expectations.

1.2.6. Adverse event reporting

Adverse side effects will be described and analyzed as a secondary outcome in the primary paper, as described in section 1.1.8. Specifically, medication side effects will be measured with the Dosage Record & Treatment Emergent Symptom Scale (DOTES). Frequencies of the most common adverse events will be tabled and reported if present in more than one subject in either of the study groups.

1.2.7. Descriptive statistics for outcomes measures

The primary and secondary outcomes as listed in section 1.1.8 will be described by treatment group and time point. Means and standard deviations or medians and interquartile ranges will be used for continuous variables.

1.3. Data Analysis Plan – Inferential analysis

1.3.1. Aims of formal inferences (overview)

The study analysis and publication plan will follow CONSORT guidelines. This statistical analysis plan will be agreed before any inspection and analysis of post randomisation assessments.

We powered our study to ask whether citalopram added to methylphenidate improves irritability symptoms and functional impairment over placebo added to methylphenidate. The formal statistical analyses will estimate the differences in relevant variables between patients randomized to citalopram added to methylphenidate compared to patients randomized to placebo added to methylphenidate, by intention to treat. That is, all randomized patients will be included in the analyses.

Group difference estimates and associated 95% confidence intervals will be reported. All data preparation and analysis for the primary paper will be blind to treatment group. If any of the data contain information that may disclose blindness, these data will be re-coded before analysis. The overall significance level will be 5% (two-sided) for the primary and secondary outcomes.

Details on the methods for handling missing data are given in sections 1.3.3.

Sensitivity analyses will be used to assess the robustness of conclusions; please refer to section 1.3.4 for details of the planned sensitivity analyses.

No interim analysis is planned.

1.3.2. Analysis of the primary outcome

The analysis population will include all randomized patients. The primary outcome is improvement of irritability as measured with CGI, see section 1.1.8.

To test the treatment effect of adding citalopram to methylphenidate vs adding placebo, a multilevel mixed-effects growth curve regression will be used. Specifically, given the multilevel structure with repeated assessments clustered within subjects, multilevel mixed models will be fitted. For the analysis of the CGI-I the growth curve model will be fitted using the `xtmixed` routine of the Stata statistical program, with restricted maximum likelihood (REML) estimation and an exchangeable covariance matrix for the covariances of the errors of the repeated measures. The fixed part of the model will include the baseline value of the outcome variable, any randomization stratification factors, treatment group, week as measure of time, and the interaction of group x week. The post-estimation `lincom` will be used to estimate the group difference at 8th week and its 95% confidence interval. Distributional assumptions will be checked by the use of Q-Q plots of residuals, and variables will be transformed where required.

The post-estimation `lincom` will be used to estimate the group difference at the 8th week and its 95% confidence interval on the logit scale. To assist in interpretation, this conditional or subject-specific effect estimate (and its CI) will be translated to an approximate, but more easily understood, marginal or population average estimate. Estimates of the group difference for weeks 1 to 8 will be plotted.

The same model will be applied for the CGI-S and other continuous secondary outcomes; depressive symptoms (CDRS) and anxiety symptoms (PARS) and the differences

Trial response will be defined as a CGI-I score less than 3 at the trial endpoint will be reported. An efficient estimate will be obtained by fitting a growth curve model of the same form as that for the CGI-I score, but for the repeated binary response fitted by maximum likelihood using adaptive quadrature in the Stata program `gsem`, with binomial family and logit link function. The model will include a random intercept. The fixed part of the model will include the CGI-S at baseline, treatment group, week as measure of time, and the interaction of group x week (a test for a quadratic term will be carried out) and will covary by any randomization stratification factors. The post-estimation `lincom` will be used to estimate the group difference at the 8th week and its 95% confidence interval on the logit scale. To assist in interpretation, this conditional or subject-specific effect estimate (and its CI) will be translated to an approximate, but more easily understood, marginal or population average estimate. Estimates of the group difference for weeks 1 to 8 will be plotted.

Frequencies of the most common adverse events will be tabled and reported if present in more than one subject in either of the study groups.

1.3.3. Missing Data

Account for missing measures will be made under an assumption of a missing-at-random mechanism. Since all remaining variables in the analysis are acquired prior to randomization there should be no further missing data.

1.3.4. Sensitivity analysis

Sensitivity analysis will be undertaken by replicating the main analyses using the Last Observation Carried Forward method for the treatment of missing data.

References