

**Protocol:**

**L-methylfolate supplementation to OROS-Methylphenidate Pharmacotherapy in ADHD: A Double-Blind,  
Placebo-Controlled, Randomized Clinical Trial**

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## I. BACKGROUND AND SIGNIFICANCE

### **There is need to improve management of Attention Deficit Hyperactivity Disorder**

Attention-deficit hyperactivity disorder (ADHD) is a neurobiological disorder associated with high levels of impairment in adulthood<sup>1-4</sup>, and is estimated to affect up to 5% of adults worldwide<sup>5-7</sup>. While currently approved pharmacotherapies for adults with ADHD are often effective, there are limits to their clinical utility. Stimulants are the mainstay of treatment for adults with ADHD due to larger effects than nonstimulants on ADHD<sup>8-11</sup>. Two decades of study by our research team and others, including controlled studies of stimulant medications and open studies of tricyclic, monoamine oxidase inhibitor, and atypical antidepressants, reveal that 20-50% of adults with ADHD are considered pharmacologic nonresponders [Wender, 1998 #24880; Wilens, 1998 #10538; Biederman, 2010 #24878]. Moreover, adults who are considered responders clinically often show a 50% or less reduction in the core symptoms of ADHD<sup>12</sup>. In addition to residual ADHD symptom burden, pharmacologically-treated patients also have residual EFD burden. For example, In a recent study of robust open label dosing with the amphetamine lisdexamfetamine, 40% of adults with ADHD were considered to have unresolved and clinically significant impairment in essential elements of behavioral control [Brown, 2010 #25825].

### **L-methylfolate is a medical food that may support catecholamine activity**

L-methylfolate (also known as 5-methyltetrahydrofolate) is identified by the FDA as a medical food. A medical food, by FDA definition, is a specially formulated product with components that are “generally recognized as safe” [Section 5(b) of the Orphan Drug Amendments (21 U.S.C. 360ee)]. L-methylfolate is approved as Deplin for suboptimal folate levels in depressed individuals or hyperhomocysteinemia in schizophrenia [Deplin [package insert]. Covington, LA: PamLab, L.L.C.; 2011 May].

Conventional therapies for ADHD are thought to work in part through reuptake blockage and/or increased release of the catecholamines dopamine and norepinephrine<sup>13, 14</sup>. Because of its role in the synthesis of the monoamine neurotransmitters serotonin, dopamine, and norepinephrine, supplementation with L-methylfolate could support higher levels of these neurotransmitters. Specifically, folate influences the rate of synthesis of tetrahydrobiopterin, which is a cofactor in the hydroxylation of phenylalanine and tryptophan – rate-limiting steps in the formation of the catecholamines dopamine, serotonin and norepinephrine<sup>15</sup> [Stahl, 2008 #25823].

Furthermore, L-methylfolate is actively transported across the blood-brain barrier. Once it crosses this barrier, L-methylfolate may bind to presynaptic glutamate receptors, where it might modulate release of catecholamines or other neurotransmitters<sup>16</sup>.

The hypothesis that L-methylfolate supplementation can improve mental health through effect on catecholamines is supported by evidence that L-methylfolate may aid depression symptoms, both in combination with antidepressant treatment and as monotherapy. Improvement in depressive symptoms has been observed in individuals with both normal and low folate levels [Fava, 2009 #25817; Godfrey, 1990 #25819; DiPalma, 1994 #25824; Passeri, 1993 #25820]. A recent chart review demonstrated that addition of either 7.5 mg or 15 mg of L-methylfolate supplementation to an antidepressant was associated with greater and faster reduction in depression symptoms. Over two and a half times as many individuals experienced a  $\geq 2$ -point improvement in Clinical Global Impression Severity ratings, and occurrence of major improvement occurred 43% faster<sup>17</sup>. In two recently completed multi-center double-blind placebo controlled trials, 223 patients determined to be inadequately responding to an SSRI for depression were given either L-methylfolate or placebo. L-methylfolate supplementation at 15 mg was associated with greater response rate (defined as 50% reduction in Hamilton depression scale rating) and reduction in depression symptoms. Only one patient that had an undetected history of bipolar disorder discontinued the trial, due to mood elevation<sup>18</sup>. Furthermore, evidence from these trials suggests that L-methylfolate may be particularly effective in the presence of particular biomarkers, such as a body mass index (BMI) greater than 30 kg/m<sup>2</sup><sup>19</sup>.

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Because L-methylfolate could facilitate reduction of ADHD symptoms via effects on catecholamine levels, we propose to conduct a double-blind clinical trial enrolling and exposing 40 adults with ADHD through midpoint of the study with an enrollment cap of 50 subjects. Half will be receiving standard OROS-methylphenidate treatment, and half receiving OROS-methylphenidate augmented by L-methylfolate. We thus propose to study augmentation of standard of care treatment. We would start both agents simultaneously, and monitor change in ADHD symptoms as well as adverse events weekly over six weeks, and then at nine and twelve weeks. Six weeks is a typical interval over which stimulant effect on ADHD may be seen, and we will extend observation to 12 weeks to measure L-methylfolate effects that might occur during a reasonable timeframe for clinical intervention.

## II. SPECIFIC AIMS

**Aim 1: Assess the safety of L-methylfolate in the treatment of ADHD among stimulant treated ADHD adults.** Hypothesis 1: L-methylfolate will be well tolerated when used in combination with OROS-methylphenidate for treating adults with ADHD. Adverse events occurring during combined use of L-methylfolate plus OROS-methylphenidate will be similar to those experienced by participants on OROS-methylphenidate alone.

**Aim 2: Assess effect of L-methylfolate on ADHD symptoms and associated features in stimulant treated ADHD adults.** Hypothesis 2: Compared to OROS-MPH treatment alone, L-methylfolate supplementation of OROS-methylphenidate treatment will yield a greater or more rapid reduction of (2a) ADHD symptoms (as measured by the AISRS and CGI), (2b) symptoms of executive dysfunction (as measured by BRIEF-A subscales) and (2c) functioning (as measured by the GAF). These are reasonable hypotheses given that OROS-methylphenidate and other stimulants are not fully effective in treating ADHD symptoms <sup>20</sup>.

## EXPLORATORY AIMS

**Aim 3: Assess whether biomarker measurements predict response to L-methylfolate.** As detailed elsewhere in this protocol, ongoing research suggests that biomarkers, including body-mass index, may be suitable for predicting response to L-methylfolate augmentation in depression. In this protocol, we detail storage of blood samples suitable to explore biomarker-related hypotheses. Lists of biomarkers of interest (both serum biomarkers and genetic biomarkers) for this study have been provided as attachments.

## III. SUBJECT SELECTION

We plan to enroll up to 50 subjects in the study. We will recruit subjects from the pool of existing subjects and new referrals to the Pediatric Psychopharmacology and Adult ADHD Program at the MGH. If a potential subject's clinician ascertains that the patient has an interest in study participation, the clinician will offer contact information for the study to him or her. The patient can then contact the study coordinator independently for more information on the actual study. If a subject is enrolled from among an investigator's own patients through the aforementioned referral process, the process of informed consent must be completed by a physician colleague who is on the approved study staff and whom the potential subject has not seen privately. Under no circumstances will a physician investigator complete informed consent with his or her own private patient. All subjects that enter the study will undergo standard screening and diagnostic procedures. Clinical records are not scanned in order to recruit subjects. Subjects who have completed a previous medication trial in our program may be eligible to participate in this study. Other medical records on a subject will not be used at any point.

The majority of subjects referred to our program first participate in our general screening protocol entitled, "Screening Protocol for Adults with Attention Deficit Hyperactivity Disorder" (Protocol # 2002-P-001856). After

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participating in this screening protocol, subjects are assigned to specific studies based upon eligibility requirements (i.e. age, prior medication efficacy or tolerability).

Our study is designed to allow a future exploratory analysis of whether biomarkers (serum biomarkers, genetic biomarkers, and body mass index (BMI)) predict response to L-methylfolate. Because we wish to have an adequate sample of adults with biomarkers of interest, including BMI, we will enroll all eligible adults, and assess midway through enrollment whether the number of individuals with biomarkers of interest is projected to be sufficient for the analysis. If necessary, we will submit an amendment to increase enrollment to ensure the number of participants will be sufficient for the analysis <sup>21</sup>.

### **Study Entry Criteria**

#### **Inclusion**

1. Male or female adults ages 18-55 years of age.
2. A diagnosis of childhood onset ADHD, meeting all but the age of onset criteria according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [American Psychiatric Association, 2000 #23616] (DSM-IV), based on clinical assessment. Childhood onset will be defined according to established research criteria, requiring onset of two symptoms of inattentive or of impulsive/hyperactive traits by the age of 12 <sup>22</sup>.
3. A score of 24 or more on the Adult ADHD Investigator Symptom Report Scale (AISRS).

#### **Exclusion**

1. A history of non-response or intolerance to methylphenidate at adequate doses as determined by the clinician.
2. A history of intolerance to L-methylfolate supplementation.
3. Pregnant or nursing females.
4. Serious, unstable medical illness including hepatic, renal, gastroenterological, respiratory, cardiovascular, endocrinologic (thyroid), neurologic (seizure), immunologic, or hematologic disease.
5. Glaucoma.
6. Clinically unstable psychiatric conditions including suicidality, homicidality, bipolar disorder, psychosis, history of or current marked anxiety, tension or agitation potentially exacerbated by a stimulant, or lifetime history of any other clinically serious condition potentially exacerbated by a stimulant, such as mania or psychosis.
7. Significant impairment due to tics, based on clinician judgment.
8. A family history or diagnosis of Tourette's syndrome
9. Current (within 3 months) DSM-IV criteria for abuse or dependence with any psychoactive substance other than nicotine.
10. Multiple adverse drug reactions.
11. Any other concomitant medication considered to be effective for management of ADHD; individuals on stable treatment with agents with central nervous system activity will be allowed to participate, as detailed in the Concomitant Medication portion of the protocol.
12. Current use of MAO Inhibitor or use within the past two weeks.
13. Investigator and his/her immediate family; defined as the investigator's spouse, parent, child, grandparent, or grandchild.
14. Use of supplemental folic acid greater than 400 mcg per day, L-methylfolate, or Omega-3 Fatty Acids greater than 800 mg per day within two weeks prior to the baseline study visit.

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Subjects need not be methylphenidate-naïve; however, no individual will be removed from an effective and stable treatment regimen for the purposes of participating in the current study.

#### **IV. SUBJECT ENROLLMENT**

Informed consent will be obtained prior to the performance of any protocol procedures and prior to administration of study drug. The informed consent document will be used to explain in simple terms the risks and benefits of study participation to the subject. The nature of the study will be fully explained to the subject by a board-certified physician who is either the primary investigator or a co-investigator. The subject will be encouraged to ask questions pertaining to their participation in the study and the subject may take as much time as they feel necessary to consider his/her participation in the study as well as consult with family members or their physicians. Participation in this study is voluntary and the subjects may withdraw from the study at any time. The IRB-approved informed consent documents will be signed and dated by the subject and the physician obtaining consent, and a copy of this document will be provided to the subject.

#### **V. STUDY PROCEDURES**

We will conduct a 12-week, double blind, placebo-controlled, randomized clinical trial to compare efficacy and tolerability of L-methylfolate as a supplement to OROS-methylphenidate (OROS-MPH) in ADHD adults. We will randomize 20 subjects to L-methylfolate plus OROS-MPH and 20 to placebo plus OROS-MPH. This is ecologically valid because long-acting stimulants are first line treatments for ADHD.

After providing study information and obtaining IRB approved informed consent, participants will undergo a comprehensive assessment including a psychiatric assessment reviewing current and lifetime DSM-IV Axis I conditions, medical history including history of any cardiac symptoms or abnormalities reported on routine clinical exams, and a neuropsychological evaluation that can be completed at evaluation or baseline. If a patient has never had a cardiac physical exam a clinician will conduct one. The information obtained at this visit will be reviewed to assure that all inclusion and exclusion criteria are met prior to receiving study medication at the baseline visit. Subjects who do not meet all the criteria for enrollment after these assessments will be discontinued.

We anticipate that subjects may enter this trial following completion of withdrawal from other protocols in our office, and that there may be procedural overlap. So as to not burden subjects with redundant time commitments, we will use the following *diagnostic* data previously collected: If a subject has completed an evaluation with one of the study clinicians within the previous 90 days prior to entrance into this study, they will not be asked to repeat any overlapping diagnostic procedures. With subjects' permission, we will use the diagnostic data that had been previously collected. However, the study clinician will review the interval time period to assess for clinically significant medical or psychiatric history, to ensure that the subject meets appropriate study entrance criteria.

Any subjects taking medication exclusionary to the study must be tapered off this medication prior to baseline visit for the length of 5 half-lives of the medication, corresponding to 95% of the agent leaving the participant's system), plus sufficient time to assess the eligibility of the participant off medication. Only subjects with inadequate response to their current treatment will be tapered from medication. Subjects will not enter the study if it would require tapering a medication that is optimally and comfortably managing a clinical concern. Medication tapers will be monitored by the study clinician in agreement with the research subject and in consultation with the prescribing physician.

Participants who fulfill the inclusion and exclusion criteria will be randomized to receive either OROS-methylphenidate and placebo or OROS-methylphenidate and L-methylfolate treatment for the period of 12 weeks. We will create the randomization schedule with the RALLOC procedure from STATA.

Vital signs (blood pressure, pulse, weight) will be measured at every visit. Height, waist circumference, and body mass index will be measured at baseline and at the end of the study. An EKG will be conducted at the beginning and the end of the study to monitor cardiac safety. A urine drug screen will be performed at evaluation, week 6, and week 12. If the participant is found to have taken an illicit drug, he/she will have a discussion with the doctor

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to determine if he/she can be in the study; subjects will be discontinued if there is suspicion of ongoing substance use. Females who are able to have children will also have a urine pregnancy test at evaluation, week 6, and week 12. If a participant has a positive pregnancy test she will not be able to take part in the study. Female subjects of childbearing potential must agree to use a medically acceptable form of birth control (such as male for female condoms with or without spermicidal agent, diaphragm or cervical cap with spermicide, medically prescribed IUD, hormonal contraceptives like birth control pills, or abstinence) while they are receiving study medication and for 1 month after the last dose of study medication. In the event that a subject becomes pregnant, we will ask the subject's permission to obtain information about the outcome of the pregnancy and the condition of the newborn. Those subjects who terminate study participation before the completion of the study will be asked to complete all tasks scheduled to take place on the final study visit at the time of study discontinuation.

Subjects will be evaluated at weeks 1, 2, 3, 4, 5, 6, 9 and 12 in the office, with optional phone contact between these visits. The need for phone contact between visits will be established by the clinician at office visits, or by needs of the subjects as they arise. At each office visit assessment of safety and efficacy will be obtained by administering measures of efficacy (CGI at every visit excluding the screening visit, AISRS at every visit, and GAF at baseline, week 6 and study endpoint), tolerability (adverse events), and safety (vital signs). Neuropsychological assessments will be repeated at study endpoint.

Although every effort will be made to encourage subjects to keep regularly scheduled appointments, in the event that a subject is unable to come into the office within a reasonable timeframe of a scheduled visit, and the treating research clinician feels that subject safety will not be jeopardized by doing so, the clinician can conduct the visit with the subject over the telephone. However, study evaluation visit, baseline visit, mid-point visit (week-6) or the final study visit may not be conducted over the phone. Additionally, phone visits may not replace scheduled office visits for two consecutive visits. This interval of office visits with phone contact as needed has proven utility in both clinical care and in a recent methylphenidate trial conducted in adults at our research unit. If a study visit occurs over the phone, all assessments and rating scales for that visit will be conducted by phone, excluding vital signs, as these can only be collected in person and links to the subject rating form may be sent to the subject in an encrypted email for remote completion.

### **Collection of blood sample for future biomarker analysis**

We are aware of recently completed research and ongoing data analysis that suggests that particular biomarkers may predict clinical response to L-methylfolate augmentation. As such, we intend to collect blood samples from subjects to conduct analyses on some or all of the biomarkers listed in the protocol attachments.

After informed consent has been obtained, a single blood draw will be performed for serum and plasma biomarkers. A blood sample of 20ml (approximately 1.5 tablespoons) following overnight fasting will be drawn at the screening visit or baseline visit. From this sample, we will prepare three types of blood samples suitable for the analyses we anticipate: plasma (suitable for possible analysis of homocysteine, hs-CRP, SAME, ADMA, MDA, and F2-isoprostane), serum (suitable for possible analysis of folate, vitamins B12 and B6), and whole blood hemolysate (suitable for possible analysis of red cell folate). These blood samples will be prepared by our department and will be stored in Pediatric Psychopharmacology on Warren 6, or delivered to the Brigham Research Assay Core (BRAC) lab at BWH, while other samples formerly assayed by Dr. Sluss' lab have been transferred to secure freezers on Bulfinch 5 until a) biomarker analyses are completed or b) samples are no longer suitable for biomarker analysis or of use to the current project and are destroyed. The samples will then be sent to Dr. Raina Fichorova at BWH for aliquoting of serum and further analyses. Dr. Fichorova's lab will prepare an aliquot for transfer to Dr. Robert Cabrera's lab at Dell Medical School in Austin, Texas for analysis for presence of antibodies to the folate receptor. Unique identifiers will be linked to the aliquots in a locked password protected database which only approved study staff will have access to. All efforts will be made to protect subject privacy, and samples will be labeled with codenames and medical record numbers. The sponsor will not have access to information that identifies participants' samples. Results from laboratory testing will

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become a part of the subjects' MGH medical records, however no information regarding participation in the study will become a part of the medical record. In the event that a subject completes screening procedures but is found ineligible for participation in the clinical trial, their blood samples will be destroyed.

Upon signing consent for the study, subjects will also be given the option of providing an additional 10 mL sample (about 1 tablespoon) during their blood draw that will be suitable for future analysis of MTHFR genetic polymorphisms. The genotyping of these samples will be conducted at the Psychiatric & Neurodevelopmental Genetics Unit (PNGU) at MGH, under the supervision of Dr. Jordan Smoller, M.D. Samples will be stored at PNGU in the Simches Research Building until the proposed biomarker analyses are completed, or samples are no longer suitable for analysis, after which they will be destroyed. This genetic sample will be collected for research purposes only, and no individual results will be given back to study participants. Any record of participation in the genetic analysis will not be included in the subject's medical record. Those subjects who choose not to provide a sample for genetic analysis may still participate in the study. Furthermore, it will be explained in the consent form that, should a subject choose to provide a sample for genetic analysis, he/she may request that their samples be destroyed at any time by contacting a member of the study staff. If a subject is found ineligible after completing screening procedures, their sample will also be destroyed.

Samples for genetic analysis will be labeled with codes only. The key to this code will be maintained by the study coordinator in a password-protected, encrypted file, and the sponsor will not have access to this document. In the event that a re-draw is recommended after DNA extraction, PNGU will notify a member of the study staff. At that time the clinician will determine if the subject should be contacted for a second sample; subjects will not be required to provide a second sample if they do not wish to do so.

A complete list of the possible biomarkers to be analyzed using these blood samples is included as an attachment.

**During the study, the following, assessments and instruments will be used:**

Brief neuropsychological measures:

- Wechsler Abbreviated Scale of Intelligence (WASI-II) Vocabulary and Matrix: to calculate verbal, performance, and full-scale IQ. If a subject has completed a neuropsychological evaluation within the previous year prior to entrance into this study, we will use the previously collected IQ score, with their permission.

Cambridge Neuropsychological Test Automated Battery (CANTAB):

CANTAB is a computer-based system designed to look at frontal lobe (executive functioning). Select subtests will include the following:

- Spatial Working Memory (SWM), tests comprehension, learning and reversal.
- Stockings of Cambridge (SOC), assesses spatial planning and motor control.
- Intra-Extra Dimensional Set Shifting (IED), tests rule acquisition and attentional set shifting.
- Reaction Time (RTI), measures speed of response.
- Rapid Visual Information Processing (RVP), tests sustained visual attention.
- Affective Go/No-go (AGN), assesses information processing biases for positive and negative stimuli.
- Verbal Recognition Memory (VRM), assesses immediate free recall, and immediate and delayed recognition memory

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- Subjects will complete a brief interview after the informed consent process to obtain demographic information including: socioeconomic status, educational history, occupation, marital status, smoking status, past head injuries, and past traumas.

Clinician rated assessments:

- ❖ DSM-IV Global Assessment of Functioning (GAF) scale. The GAF will assess global functioning using a scale from 1 (worst) to 100 (best).
- ❖ Clinical Global Impressions (CGI) scale for ADHD. The CGI is a measure of illness severity, improvement, and efficacy of treatment.
- ❖ DSM-IV based Adult ADHD Investigator Symptom Rating Scale (AISRS). Each of the individual symptoms of ADHD is rated 0 to 3 on a scale of severity.
- ❖ Hamilton Depression (HAM-D) and Anxiety <sup>23</sup> (HAM-A) Scales to evaluate depression/anxiety symptoms.
- ❖ Adverse Experiences and Concomitant Medications.

Subject rated scales:

- ❖ The 18-item Adult ADHD Self-Report Scale (ASRS) to evaluate frequency of ADHD symptoms on a scale of 0 to 4.
- ❖ The 86-item Behavior Rating Inventory of Executive Function – Adult Form (BRIEF-A) to assess levels of executive function deficits.
- ❖ The Adult Self-Report Form <sup>24</sup> (ASR) to measure a wide range of psychiatric syndromes (i.e., depressive problems, anxiety problems, antisocial personality problems) in adults. The ASR provides dimensional scale scores for each syndrome that are age- and gender-normed.
- ❖ The Social Adjustment Self Report Questionnaire (SAS) to measure overall social adjustment and satisfaction.
- ❖ The 16-item Quality of Life Enjoyment & Satisfaction Questionnaire (Q-LES-Q) to measure overall satisfaction across different aspects of daily life.
- ❖ The 8-item Emotional dysregulation subscale of the Barkley Current Behavior Scale—Self-Report (CBS DESR) to measure emotional reactivity.
- ❖ The 25-item Endicott Work Productivity Scale (EWPS) to measure behaviors and feelings likely to reduce productivity and efficiency in work activities.

Study participants may request the results of their cognitive testing. In this case, the subject will receive a letter providing a basic interpretation of the results and referring the subject to the department's supervising neuropsychologist for any questions or concerns.

Data will be collected using StudyTRAX. StudyTRAX is an electronic data capture system that streamlines data collection and management and ensures data integrity. StudyTRAX software allows researchers to design and implement study surveys for collected, stored, retrieving, and manipulating data electronically.

Participants and/or research staff enter survey responses into electronic assessment forms, and the responses are then transmitted securely via encrypted connection and stored in a secured database. This electronic data capture obviates the need for subsequent data entry by staff, thus minimizing human error. However, it is still possible that rating scales will be collected in paper form in the case that StudyTRAX is not working or unavailable.

These surveys are completed securely via the internet by using any device with standard web access and browsers. For this study, participants and staff will complete the electronic assessments on computer terminals at the

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research site under the supervision of study staff. If the study visit has been conducted over the telephone or if subjects need to leave before completing scales, subjects may have links to subject rating forms securely emailed to them for remote completion. The links will be unique to the subject completing the questionnaires, preventing them from accessing any other data stored on the password-protected database. Only those subjects who receive the links via email will be allowed to access the forms.

In the event that the electronic data capture system is unavailable during a study visit (due to technical issues), rating scales will be collected in paper and then entered into the program manually once the system becomes available.

For quality control purposes, audio of clinician-administered measures completed during the visits may be recorded, with subjects' permission. These recordings will be used to monitor quality control and inter-rater reliability in this study by the PI. Each audio file will be coded with subject initials and number to maintain confidentiality. These tapes will be de-identified and stored in a password-protected file.

Upon completion of the study, participants can choose to pursue follow-up care, as possible, at our MGH practice or continue treatment with their primary care physician. Study clinicians may also offer psychiatric referrals to treaters in their communities.

### **Study Medication**

At the baseline visit, subjects will receive a prescription for OROS-MPH and will be randomized to receive either L-methylfolate or placebo (under double blind conditions).

OROS-MPH and L-methylfolate/placebo will be administered concurrently. OROS-MPH will be openly prescribed, starting with an initial dose of 36 mg/day. OROS-MPH will be titrated to optimal response (not exceeding a maximum daily dose of 1.3 mg/kg or 108 mg/day, whichever is lower), according to clinician judgment, during the first six weeks of the trial. During this titration period, dose will be increased on a weekly basis in 18-36 mg/day increments, according to clinician judgment, with the goal of obtaining a well-tolerated and effective dose. At any time, the dose may be reduced if adverse effects present or if the subject discontinues treatment. At subsequent visits, a higher dose may be resumed if tolerated.

L-methylfolate dosing will start and remain at 15 mg/day of L-methylfolate for the duration of the study in the form of PAMLAB brand L-methylfolate. PAMLAB is also able to make a matched placebo product and will provide us with a detailed Certificate of Analysis attesting to the contents of the caplets. Our proposed dosing is consistent with the current indication for L-methylfolate as a medical food. The study clinician will be responsible for dispensing the L-methylfolate at our research office. In order to maintain the blind, the MGH Clinical Trials Pharmacy will prepare the L-methylfolate drug/placebo, and the study clinician will not know whether he/she is dispensing active drug or placebo. After the study, subjects can obtain L-methylfolate by prescription from their current treater. Study clinicians, in cooperation with the subject and the subject's treater, may develop a plan for continued L-methylfolate treatment after the completion of the study.

At each visit, measures of safety and effectiveness will be administered and subjects will be evaluated for response and side effects to the treatment. To assess and ensure drug accountability and compliance, study medication will be returned and counted at study visits.

Information regarding subjects' status of assignment to medication or placebo will be available at all times through the MGH Clinical Trials Pharmacy. In addition, the randomization list will be available to the investigator at all times, in case of emergency.

### **Concomitant Medications / Treatments**

A detailed past and present treatment history will be taken as part of initial evaluation. Participants treated with any psychotropic medication not thought to help ADHD, such as SSRIs, may be eligible to participate, provided that they have been on a stable, effective dose for at least two months prior to study enrollment, and have scores within the mild range on the HAM-A and HAM-D scales (<17 on the HAM-A scale and <13 on the HAM-D

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scale) at baseline. Subjects must also remain on the same dose of this medication throughout participation. Any other Concomitant medications with FDA indications for the treatment of ADHD or that have probable efficacy for the treatment of ADHD as per clinician judgment are not allowed in this study. Any agents that would add additional risk which could not be managed using existing study procedures will be exclusionary. No subject will be tapered from medication that is useful to him or her. Non-pharmacological treatments such as individual, family or group therapy will be allowed if they were in place before the patient joined the study. The patient's therapy regimen must remain the same throughout the study. If a subject is asked to stop a medication with central nervous system activity for participation in the study, sufficient time will pass off the medication prior to baseline visit, based on the pharmacokinetics of the agent, to ensure that it has been eliminated from the patient's system.

### **Study Discontinuation Criteria**

Subjects who: 1) develop intolerable AE(s) despite dose adjustments; 2) have (a) clinically relevant serious AE(s) as determined by the investigator including changes in vital signs; 3) have worsening ADHD symptoms (much worse or very much worse as rated on CGI-Improvement at two consecutive visits); or 4) have emergent psychosis, suicidality, substance use, or worsening mood and/or anxiety (much worse or very much worse per clinician assessment at weekly visits); 5) are non-adherent to study procedures or withdraw from the study; 6) intend to be or become pregnant will no longer continue in the study. If study participation is discontinued due to safety reasons, participants will receive two follow-up visits, giving adequate time for appropriate psychiatric referrals to treaters in their communities.

## **VI. BIostatistical Analysis**

Data processing and management will follow procedures developed by the investigators and used in ongoing studies. Up to 50 subjects will be randomized (1:1) into one of two treatment groups: the L-methylfolate plus OROS-MPH, or placebo plus OROS-MPH. The MGH Clinical Trials Pharmacy will be responsible for creating and maintaining the study randomization schema. Changes in outcome ratings within and between study groups over time will be tested with longitudinal generalized estimating equation (GEE) regression models estimated using STATA within the framework of the general linear model (GLM). Each model will predict outcome scores from treatment group (binary predictor), study visit (ordinal predictor) and the group by visit interaction. All analyses will be intention to treat (ITT). While we hope to find clinically significant improvement in ADHD symptoms, as outlined below, this is a pilot study and is not designed to show statistically significant change.

Our primary test of Hypothesis 1 will be review of the occurrence of moderate or severe adverse events. Hypothesis 2 examines side effects associated with the combined use of L-methylfolate plus OROS-MPH. The prevalence of binary side effects reported over the course of the trial (i.e. for each side effect, the cumulative sum from the first assessment to endpoint) will be compared between groups using Poisson regression at study endpoint. Hypothesis 3 predicts that compare to OROS-MPH treatment alone, L-methylfolate acid treatment as a supplement to OROS-methylphenidate treatment will yield a greater reduction of ADHD symptoms (as measured by the AISRS and CGI), symptoms of executive dysfunction (as measured by BRIEF-A subscales) and functioning (as measured by the GAF). The AISRS will be used as the primary outcome measure for improvement in ADHD symptoms. This hypothesis predicts a significant difference in these measures between groups at study endpoint, and/or a group by visit interaction in these measures. We will compare continuous measures with longitudinal GEE models. We estimate 0.89 power to detect a medium effect size (Cohen's  $d=0.5$ ) given a repeated measures design with one baseline measurement and eight follow-up measurements, correlation of 0.7 between measurements, and a two-sided test with alpha set at 0.05. Although less than the effect size for treatments of ADHD symptoms by non-stimulants ( $\sim 0.7$ ) or stimulants ( $\sim 0.9$ )<sup>8</sup>, an effect size of 0.5 is similar to what is seen for the effects of antidepressants for depression<sup>25</sup> and thus would be considered clinically significant.

## **VII. RISKS AND DISCOMFORTS**

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All efforts are made to minimize risks to subjects. Consistent with good clinical practice, safety will be monitored by the Principal Investigator, and will reflect the oversight of co-investigator study clinicians. Adverse events will be recorded and reported according to institutional policies. Risks of study medication have been incorporated into the exclusionary criteria for this proposal.

Study clinician evaluation and subject questionnaires: Some questions may make subjects feel uncomfortable. Subjects may refuse to answer any question. In the event that a participant reports risk of harm to himself or herself, or to another person, study clinicians will assess the level of risk, and take appropriate actions, including disposition of an immediate referral to a local Psychiatric Emergency Room.

Study Medication – L-methylfolate: No COMMON side effects have been reported in FDA documentation about the medical food L-Methylfolate. Rarely, severe allergic reactions to L-methylfolate might occur, including rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue.

Study Medication – OROS-MPH: The medication used in this study will be one of the most commonly prescribed stimulant class of medication; the extended duration methylphenidate, OROS-MPH (Concerta®). OROS MPH is currently FDA-approved for ADHD in children, adolescents and adults. Commonly-observed side effects associated with the use of OROS MPH include difficulty falling asleep, low appetite, headaches, stomachaches, nervousness, and dizziness. Side effects tend to be mild. Rare, but serious side effects of OROS MPH include seizures, eyesight changes, and blockage of esophagus, stomach or intestine. There are also reports of changes in behavior or cognition with stimulant use, including psychotic symptoms, and aggression/hostility. Persons with a history of tics may experience return of symptoms. OROS MPH is a federally controlled substance which can be abused or lead to dependence. Heart-related problems including sudden death, stroke and heart attack, have been reported with use of methylphenidate and other stimulant medicines. Recently published controlled data from our group has demonstrated efficacy and tolerability of OROS MPH in a large sample of healthy adults with ADHD (Biederman et al, 2006). Dosing for this protocol is consistent with our clinical experience with this medication.

Blood Draw: There is a risk of bruising or pain where the blood draw is conducted. There is small risk of infection, lightheadedness, or fainting as a result of a blood draw.

Genetic Information: There is a risk that information about taking part in a genetic study may influence insurance companies and/or employers regarding a subject's health. Subjects will be informed of this risk, and it will be explained that they can reduce this risk if they do not share information about their study participation. In addition, all efforts will be made by the study staff to maintain confidentiality. DNA samples will be coded with ID numbers, and they key will only be accessible by study staff.

### **Confidentiality**

All research-related records initiated as a result of a subject's participation in this study that reveal the subject's identity will remain confidential except as may be required by law. Subjects will be informed that clinical laboratory testing for this study will become part of a subject's Massachusetts General Hospital medical record. However, information regarding their participation in the optional genetic analysis will not be included in their medical record. Results of urine drug or pregnancy testing will not become part of the subject's medical record. Data obtained from this study will not identify the subjects individually. Subjects will be assigned code-names and ID numbers. Data obtained from our studies may be published. Original research-related records may be reviewed by the Partners Human Research Committee, and regulatory authorities, for the purpose of verifying clinical trial procedures and/or data. Information may be held and processed on a computer. Access to these computerized records will be password protected and restricted to study staff. Subjects will only be contacted regarding future studies if they indicate that they are interested in being contacted by initialing in the specific section of the consent form.

#### **VIII. POTENTIAL BENEFITS**

There may be no direct benefit to subjects participating in this study. Potential benefits to the participants include education about ADHD, a trial of medication that could be continued after the study, and the opportunity to contribute to medical science and thus help others with similar difficulties.

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	Eval	Baseline (Visit 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 9	Week 12 (Or Drop)
Consent	X									
<b>Procedures</b>										
Blood Draw	X*	X*								
Vital (weight, pulse)      Signs BP,	X	X	X	X	X	X	X	X	X	X
Height	X									X
Urine      Drug Screen	X							X		X
Urine      Pregnancy (females only)	X							X		X
EKG	X									X
<b>Assessments</b>										
WASI	X									
CANTAB	X*	X*						X		X
Clinician Interview Inclusion/ Exclusion	X									
<b>Clinician Rated Scales</b>										
AISRS	X	X	X	X	X	X	X	X	X	X
CGIs		X	X	X	X	X	X	X	X	X
HAM-D; HAM-A		X						X		X
GAF		X						X		X
Adverse Events		X	X	X	X	X	X	X	X	X

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<b>Concomitant Medications</b>		X	X	X	X	X	X	X	X	X
<b>Patient Rated Scales</b>										
<b>Demographic Interview</b>	X									
<b>BRIEF-A</b>		X						X		X
<b>ASRS</b>		X	X	X	X	X	X	X	X	X
<b>ASR</b>		X						X		X
<b>SAS</b>		X						X		X
<b>Q-LES-Q</b>		X						X		X
<b>CBS DESR Scale</b>		X						X		X
<b>EWPS</b>		X						X		X

\* Can be completed at either evaluation or baseline visit

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