Study Protocol:
An Open-Label Treatment Trial to Assess the Short-Term Tolerability, Safety, and Efficacy of Methylphenidate Hydrochloride Extended-Release Liquid Formulation in High-Functioning Autism Spectrum Disorder Adults with Attention-Deficit/Hyperactivity Disorder

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1. BACKGROUND AND SIGNIFICANCE

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by variable presentation of difficulties with socialization, reciprocal communication, and restrictive/repetitive behaviors (APA, 2013). An increasingly higher prevalence of ASD is documented in each successive epidemiological survey and the disorder is now estimated to affect up to 2% of youth in the general population (Blumberg et al., 2013). This rise in prevalence is in part attributed to improved recognition of autism in intellectually capable populations (ADDM Network, 2012).

ADHD is the most common psychiatric disorder recognized in youth and adults with ASD and greatly add to their morbidity and dysfunction, particularly in those with intact intellectual capacity (Joshi et al., 2010, 2013; Stahlberg et al., 2004; Ryden & Bejerot et al., 2008; Ghaziuddin & Zafar 2008; Frazier et al., 2001; Wozniak et al., 1997; de Bruin et al. 2007; Sinzig et al., 2009). Youth and young adults with intact intellectual capacity constitute a majority of the psychiatrically referred ASD population (Joshi et al., 2010, 2013, [under review]; Ryden & Bejerot, 2008; Frazier et al., 2001; Wozniak et al., 1997). Nearly two-thirds (ranging from 37-68%) of clinically referred populations of adults with ASD suffer from ADHD (Joshi et al., 2013; Stahlberg et al., 2004; Ryden & Bejerot et al., 2008).

Our team of researchers has repeatedly documented striking homology in the phenotypic presentation of ADHD in youth irrespective of comorbidity with ASD, suggesting that the clinical presentation ADHD in ASD is typical of the disorder (Joshi et al., 2014 [*under review*]; Wozniak et al., 1997; Frazier et al., 2001).

As ADHD is functionally more impairing in the context of intellectual demands, the presence of ADHD in intellectually capable individuals with ASD causes significant impairment in their intellectual as well as social functioning as they usually co-function alongside typically developing peers (Joshi et al., 2014, [*under review*]). ADHD-related impairment in intellectual and social functioning is particularly disabling to those transition-age HF-ASD individuals who attend college and are therefore especially vulnerable to social and transition-related challenges.

While there is no established pharmacological treatment for the core features of ASD, there are well-established evidence-based pharmacotherapies available for the management of psychiatric disorders in typically developing individuals that frequently co-occur with ASD. Considering that ADHD is known to respond to a variety of pharmacological interventions in typically developing individuals, morbidity and impairments in autistic individuals can be minimized by identifying and offering treatments for ADHD comorbid with ASD.

In general, the psychopharmacologic treatment response in ASD populations is atypically associated with higher susceptibility to adverse effects. Treatment literature suggests that compared to general population, individuals with ASD may be more susceptible to adverse responses to stimulant medications (Campbell et al., 1972 &

1976; Stigler et al., 2004), and this susceptibility could be dose-related (Handen et al., 2000).

In clinical practice, ASD youth are routinely treated with stimulants for symptoms of ADHD and surveys suggest a steady rise in this trend (Croen et al., 2006; Langworthy-Lam et al., 2002). Of all psychotropic medications, the stimulant class - methylphenidate (MPH) in particular - is the most widely prescribed in this population (Langworthy-Lam et al., 2002; Aman et al, 1995). Although empirical evidence on the tolerability and efficacy of stimulants for managing ADHD in ASD populations is limited, MPH remains the most studied anti-ADHD medication in ASD populations (RUPP, 2005; Handen et al., 2000; DiMartino et al., 2004).

ASD youth with ADHD respond to a lower-than-expected dose of MPH (0.3mg/kg/day; Handen et al., 2000) with the magnitude of response typically less than that observed in typicals (50% vs. 70-80%; RUPP, 2005 vs. MTA, 2001). In the largest controlled trial of stimulants in an ASD population to date (which included ASD youth with impaired intellectual capacity), half of the children were reported to have experienced moderate response to oral MPH in hyperactivity and/or impulsiveness with side effects that were, in some cases, severe enough to discontinue treatment (RUPP, 2005). In this trial, the less-than-expected MPH response could be due to: 1) the presence of intellectual disability (ID; IQ<70) as a negative confounder, 2) a judgment of MPH response based only on improvement in hyperactivity/impulsiveness (where the outcome of inattentiveness could not be evaluated due to subjects' lack of verbal abilities), or 3) the assessment of hyperactivity and/or impulsivity with the Aberrant Behavior Checklist (ABC), a scale limited in capturing all of the dimensions of ADHD-related hyperactivity/impulsivity.

To date, no stimulant trial has been conducted in an ASD population without ID. Results from stimulant trials for ADHD in youth with ID are inconclusive with reports of poor (Handen et al., 1990, 1991, 1992; Aman et al., 2003) to favorable response (Pearson et al., 2003, 2004, 2004). No data is available on the role of ID on the assessment of stimulant efficacy in children and adolescents with ASD. Nonetheless, the presence of ID may confound the outcome of stimulant trials for ADHD in ASD populations.

Despite the overall lower tolerability to psychotropic medications demonstrated in ASD populations, there is no empirical evidence available on the treatment response to extended-release stimulant medications, which offer better tolerability due to a gradual mode of delivery. Clearly, there is a need for psychotheraputic agents with acceptable efficacy and tolerability profiles (taking into account mode of delivery) for the treatment of comorbid ADHD in individuals with ASD.

Quillivant XR, an extended-release liquid formulation of methylphenidate hydrochloride, offers a gradual mode of delivery that may offer improved tolerability. The liquid preparation offers tremendous flexibility for initiating at a lower dose and for titration with smaller dose increments. In addition, the extended-release liquid preparation offers an

alternative mode of oral medication delivery for individuals who are incapable of swallowing pills.

As individuals with ASD are more susceptible to adverse effects, require lower dose initiation and smaller dose titration, and are often unable to swallow pills due to sensory dysregulation, a liquid preparation of sustained-release MPH may offer better compliance and tolerability. Given that no empirical evidence on this medication in the referenced population is available, a systematic trial on the efficacy and tolerability of extended-release liquid-formulation MPH for the treatment of ADHD in intellectually capable individuals with ASD is warranted.

2. SPECIFIC AIMS

The purpose of this 6-week, flexible-titration, open-label study is to assess the tolerability, safety, and efficacy of methylphenidate hydrochloride extended-release liquid formulation (MPH-ERLF) for the treatment of attention-deficit/hyperactivity disorder (ADHD) in adults with high-functioning autism spectrum disorder (HF-ASD). Based on our central hypothesis that MPH-ERLF will be safe, tolerable, and effective in improving ADHD symptoms in adults with ASD, we propose to enroll up to 40 subjects of both genders ages 18-40 years with intact intellectual functions satisfying DSM-5 criteria for both ASD and ADHD.

Primary Objective:

- To evaluate the efficacy of MPH-ERLF for the treatment of ADHD in adults with HF-ASD

Secondary Objectives:

- To assess the safety and tolerability of MPH-ERLF short-term therapy in adults with HF-ASD
- To study the treatment effect of MPH-ERLF short-term therapy on the social cognition and executive functions in adults with HF-ASD

3. LENGTH OF STUDY

This study will last up to 12 weeks from enrollment (allowing up to six weeks from the date of consent to schedule and complete the initial screening process). Once subjects have completed the screening process and baseline characterization, they will begin the 6-week open-label trial. Subjects will be assessed on measures of efficacy and safety every week throughout the study.

4. SOURCE OF SUBJECTS

We plan to enroll up to 40 young adults in order to achieve the goal of exposing 20 subjects to the study medication. Individuals who respond to local advertising will be screened for eligibility first by the study coordinator via phone and then in person by a study clinician. We also plan to recruit participants from the referral pool of existing and new patients attending a specialty clinic for ASD at the Massachusetts General Hospital, and through advertising in local and regional media via print ads, Internet ads, and advertising posters**.** Subjects may also be recruited from Facebook advertisements. These advertisements will link to a RedCap survey where interested participants can

submit their contact information so that a member of our staff can call or email them with more information. Alternatively, our contact information will be provided so that they may call or email us directly. Our study staff will complete a study-specific phone screen with all interested participants. Participants who meet eligibility criteria will then be brought in to meet with a study clinician who will explain the study in detail and complete the informed consent process.

The Alan and Lorraine Bressler Clinical and Research Program for Autism Spectrum Disorder is a specialized ambulatory care program devoted to the assessment and treatment of individuals of all ages with ASD. It is one of only a few programs in the New England area to offer comprehensive assessment for individuals with ASD, including a complete psychiatric evaluation, psychopharmacological, neuropsychological, behavioral, and social services consultation, psycho-educational support and cognitive/behavioral therapies. The ambulatory care team consists of board-certified psychiatrists specialized in the assessment and management of ASD. Adults with ASD, the majority of whom are individuals with intact intellectual capacity and language skills, make up approximately one-third of the ASD population attending the clinic.

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 coordinator to the patient. The patient can then contact the study coordinator for more information on the trial. All subjects that enter the study will undergo standard screening and diagnostic procedures. Clinical records are not scanned in order to recruit subjects. Patients who potentially meet criteria for the study will only be contacted by their treating clinician and referred should the patient decide they wish to participate. If a patient of an investigator decides to enroll in the trial, the process of informed consent will be conducted with a co-investigator who does not treat the patient in a clinical setting. Under no circumstances will a physician investigator obtain informed consent from his or her own patient.

Subjects who have completed a previous medication trial in our program may be eligible to participate in this study, as described in the Study Design section. Other medical records on a subject will not be used at any point during this study.

5. SUBJECT ENROLLMENT

Informed consent/assent will be obtained prior to the performance of any protocol procedures including administration of study drug. The informed consent and assent documents will be used to explain, in simple terms, the risks and benefits of study participation to the subject. The Informed Consent Form will include an area where legal guardians or authorized representatives can provide informed consent for eligible dependents. In addition to the "Guardian and Authorized Representative for Adult" signature line, a line of Assent will be provided for study-participants between the ages of 18 and 40 who have legal representatives. The nature of the study will be fully explained to the subjects and/or their legal representative by a board-certified physician who is either the principal investigator or a co-investigator. The subjects and/or their legal representative 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 their participation in the study and to consult with family members or their physician. Participation in this study is voluntary and subjects may withdraw from the study at any time. The IRB-approved informed consent/assent documents will be signed and dated by the subject and/or the subject's legal representative and the physician obtaining consent.

6. SUBJECT SELECTION CRITERIA

A. Inclusion Criteria

- Male or female participants between 18 and 40 years of age (inclusive)
- Fulfills DSM-5 diagnostic criteria for autism spectrum disorder as established by the clinical diagnostic interview and ADOS
- Fulfills DSM-5 diagnostic criteria for ADHD as established by the clinical diagnostic interview and confirmed by the K-SADS-E ADHD module
- Participants with at least moderately severe symptoms of ASD as demonstrated by SRS raw score ≥ 85 and CGI-ASD severity score ≥ 4
- Participants with at least moderately severe symptoms of ADHD as assessed by AISRS score ≥ 24 and CGI-ADHD severity score ≥ 4
- Participants and/or their legal representative must understand the nature of the study. Participants and/or their legal representative must sign an IRB-approved informed consent form before initiation of any study procedures.
- Participants and/or their legal representative must have a level of understanding sufficient to communicate with the investigator and study coordinator, and to cooperate with all tests and examinations required by the protocol.
- Participant must be able to participate in mandatory blood draws.
- Participant with major mood and/or anxiety disorders will be allowed to participate in the study provided they do not meet any exclusionary criteria.

B. Exclusion Criteria

- Impaired intellectual capacity (IQ <85)
- Participant is unable to communicate due to delay in, or total lack of, spoken language development (grossly impaired language skills)
- Clinically unstable psychiatric conditions or judged to be at serious safety risk to self (suicidal risk) or others (within past 30 days).
- Subjects currently (within past 30 days) experiencing significant features of anxiety, mood, or psychotic disorder as determined per clinician judgment informed by a comprehensive review of subjects' initial psychiatric evaluation and clinical assessment.
- History of substance use (except nicotine or caffeine) within past 3 months (inclusive) or with urine drug screen positive for substances of abuse
- Subjects with a medical condition or treatment that will either jeopardize subject safety or affect the scientific merit of the study, including:
    - Pregnant or nursing females or females with a positive beta-HCG pregnancy test.

- Uncorrected hypothyroidism or hyperthyroidism.
- History of non-febrile seizures within last 1 month without a clear and resolved etiology.
- History of renal or hepatic impairment.
- Glaucoma
- Tourette's syndrome and/or motor tics
- Serious, unstable systemic illness

- Personal history of cardiac disease or a family history of non-geriatric cardiac disease or death
- Clinically significant abnormal baseline laboratory values which include the following:
  - Values more than 20% above the upper range of the laboratory standard for a basic metabolic screen.
  - Systolic and diastolic blood pressure parameters above 140 and 90, respectively.
  - Resting heart rate outside of 60-100 bpm.
  - Abnormal ECG parameters defined as QTC> 460msec, QRS>120 msec, and/or PR>200 msec.
  - ECG evidence of ischemia or arrhythmia as reviewed by an independent cardiologist.
- Participant with a history of non-response to adequate trial of methylphenidate (therapeutic dose for an adequate duration) as determined by clinician.
- History of intolerance or an allergic reaction to methylphenidate.
- Current or recent treatment (within the past 30 days) with current stimulant class of anti-ADHD medications.
- Current treatment with monoamine oxidase inhibitors (MAOIs)
- Current treatment with a first- or second-generation antipsychotic medication on a dose that has not been stable for at least 4 weeks prior to baseline visit.
- Current treatment with a psychotropic medication on a dose that has not been stable for at least 4 weeks prior to baseline visit.
- Investigator and his/her immediate family, defined as the investigator's spouse, parent, child, grandparent, or grandchild.

While stably treated or remitted hypertension is not exclusionary, any subject with a history of high blood pressure will be asked to obtain approval from their primary care physician certifying that their hypertension is stable and that they may safely begin stimulant therapy. Subjects will be informed of the cardiovascular risks of MPH, and any subject with a history of hypertension who is unwilling to consult with their current treater—or to grant study staff permission to consult with the subject's current treater—will be excluded because of the potential risks to subject safety. Per the FDA approved MPH-ERLF package insert, high blood pressure is not a contraindication of MPH therapy; however, due to the cardiovascular side effects, it is recommended that subjects with a history of high blood pressure be monitored carefully. Cardiovascular risk factors are carefully monitored throughout the study for all subjects by way of screening electrocardiograms and pulse/blood pressure readings at every office visit. Patients with current untreated hypertension are not eligible.

7. DESIGN

All data will be collected and entered into StudyTRAX, an electronic data capture system that streamlines data collection and ensures data integrity. StudyTRAX software allows researchers to design and implement study surveys electronically for collecting, storing, retrieving, and manipulating data.

Participants and/or research staff will enter survey responses into electronic assessment forms using computers at the research site. The responses will then be transmitted securely via an encrypted connection and stored in a secured database. Electronic data capture eliminates the need for subsequent data entry by staff, thus minimizing human error. However, in the event that StudyTRAX is malfunctioning, study staff will print all study instruments and study data will be collected in paper form.

Primary outcome measure will be reduction in ADHD symptoms as measured by change from baseline on the clinician-rated AISRS. Responders will be defined as those who demonstrate a ≥30% reduction in AISRS total score and CGI-ADHD-Improvement score ≤2. Safety and tolerability will be assessed by the monitoring of spontaneous treatment-emergent adverse events with the Clinician-rated Treatment-emergent Adverse Events Log (CTAE).

Secondary outcome measures will assess for treatment-related changes in associated psychopathology, social cognition, executive functions, and safety and tolerability:

- Changes in autistic symptoms as reflected by CGI-ASD and SRS-2 (Informant Report) and SRS-2 (Self-Report).
- Changes in executive functions and social cognition as reflected by CANTAB, WAIS-IV, BRIEF-A, and DANVA2.
- Safety and tolerability will be further assessed by monitoring for:
  a) Anxiety symptoms as reflected by HAM-A
  b) Obsessive/compulsive symptoms as reflected by Y-BOCS
  c) Depressive symptoms assessed by HAM-D
  d) Mania symptoms as reflected by YMRS
  e) Psychotic symptoms as reflected by BPRS

Dosing

MPH-ERLF will be titrated to the target daily dose during the first three weeks of the trial (dose optimization phase). Titration of study medication will be guided by the following flexible titration schedule, as well as by tolerability to MPH-ERLF per clinician judgment. Week 3 and onwards, subjects will be maintained on maximum achieved dose with a one-time option to decrease the dose of the study medication to the next lowest available dose per clinician judgment based on tolerability to MPH-ERLF. Based on the tolerability and safety reported by MPH-ERLF trials in youth with ADHD, the following MPH-ERLF titration schedule is proposed:

Flexible Titration Schedule

Week	Day	Dose (mg)
0	0	5
0.5	4	10
1	**8**	**20**
1.5	11	30
2	**15**	**50**
2.5	18	60
3-6	**22-42**	**Maintain on maximum achieved dose**

Enough study medication for 9 days of dosing will be dispensed at each weekly visit. To assess and ensure drug accountability and compliance, study medication will be returned and re-dispensed by the study clinician at every visit.

At each visit during the titration period, participants will be given a dosing schedule for the week, outlining daily dosing instructions and highlighting when a mid-week dose increase is scheduled to occur (barring any adverse events). Contact information of the principal investigator and co-investigators will be listed on the dosing schedule, and participants will be instructed to call or page if they are ever uncertain about dosing or experience any adverse events.

Additionally, the study coordinator will complete scheduled compliance phone check-ins each week during the titration period. These phone calls will be made the day before a scheduled dose increase in order to remind subjects of the scheduled mid-week up-titration. If, during the call, participants express concern about dosing or adverse events, the coordinator will transfer the call to a study clinician who will assess whether any dosing adjustments are needed.

Concomitant Medications/Treatments

As part of the initial psychiatric evaluation, a detailed history of past and present treatments (pharmacological and non-pharmacological) will be obtained. At each study visit, subjects will be assessed for the use of concomitant medication. The guidelines for use of concomitant medications/treatments during the study are as follows:

- Participants may continue treatment with concomitant psychotropic medications (provided no exclusion criteria are met) and must remain on a stable dose during the course of the trial.
- Subjects may take melatonin (up to 3 mg) or Benadryl (up to 50 mg) at bedtime as needed (prn) for insomnia.
- Subjects requiring initiation of acute or chronic medication treatment may be discontinued from the study if treatment is judged by the investigator to interfere with the assessment of study drug effect.
- Non-pharmacological treatments such as supportive individual, family, or group therapy will be permitted provided they were in place for a substantial period of time

(>1 month) prior to study enrollment and remain unchanged during the course of the trial.
- No new non-pharmacological treatments may be initiated during the course of the trial.

Screening Process (Week 99)
The screening process will last up to 4 hours in total (involving up to 2 visits) and includes the following components:

- Subjects will meet with a study clinician for a psychiatric evaluation and review of medical history.
- The study clinician will ask the participant about his or her symptoms of autism spectrum disorder.
- A study clinician will conduct a brief physical examination.
- Female participants of childbearing potential will complete a urine pregnancy test. If a participant has a positive pregnancy test, she will not be able to take part in the study. The study doctor will inform the participant and discuss the clinically appropriate course of action. The participant will be offered 3 follow-up visits.
- Participants will be required to give a urine sample to test for certain types of drugs. This includes prescription drugs, illegal drugs, and controlled substances (substances that may be habit-forming) that may affect behavior and that may be regulated by law. Results of the drug screen will be conveyed to the participant by the study clinician. If the results are positive for drug(s), there will be further discussion with the participant to determine if their continued participation in the trial is appropriate.
- An electrocardiogram (ECG) will be conducted.
- Blood will be drawn for laboratory tests. Clinical laboratory testing will consist of a comprehensive metabolic panel (electrolytes, liver function tests, thyroid function tests, glucose) and a complete blood count (CBC). The total amount of blood we will draw in this study is about 2 tablespoons.
- The participant's vital signs (blood pressure, heart rate, and weight) and height will be measured.
- We will ask the participant to complete a questionnaire about their ASD symptoms (SRS-2). This questionnaire takes approximately 5-10 minutes to complete.
- We will ask the participant to complete a brief demographic interview collecting information regarding socioeconomic status and history of head injury or trauma. This will take about 5-10 minutes to complete.
- The participant will complete cognitive testing (WASI) to estimate full-scale IQ. This testing will take about 30 minutes to complete.
- A trained psychometrician will conduct the K-SADS-E ADHD module with the participant to confirm diagnosis of ADHD. This will take about 30 minutes to administer.
- A trained psychometrician will conduct the ADOS with the participant to confirm diagnosis of ASD. This will take about 1 hour to administer.

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/parents/guardians 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 in the three years preceding their entrance to the study, they will not be asked to repeat these overlapping diagnostic procedures. We will use the study diagnostic data previously collected so as to not burden the subject with redundant time commitments. 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.

If the subject has completed the WASI or WAIS-IV in the 12 months preceding their entrance into this study, subjects will not be asked to repeat these procedures. We will use the data previously collected so as not to burden the subject with redundant time commitments.

Study participants and/or their legal guardians 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 them to the department's surpervising neuropsychologist for any questions or concerns.

Washout Period

After the screening period, subjects who are currently taking prohibited medications and willing to discontinue the use of their medication may do so in order to be eligible for participation in this study, if clinically appropriate per clinician judgment. Due to the increased risk for psychosis upon discontinuation of an antipsychotic and initiation of a stimulant, first- or second-generation antipsychotic medications will not be discontinued for the purposes of initiating this trial. If appropriate, medication washout will be recommended by our clinicians to participants and current providers. Clinicians will determine a washout schedule based on the half-life of the medication, the adverse effects associated with treatment and withdrawal, and an assessment of individual factors including duration on drug and dose. Our office does not take over care for the patient, but remains available during this time period. The washout schedule will be discussed with the participant and current providers.

Study Visits (Weeks 0 through 6)

Study visits will have a visit window of +/- 2 days to facilitate scheduling. 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 and parent/guardian over the phone. This will ensure that each subject will be continuously monitored by the clinician throughout the course of the study despite unforeseen scheduling circumstances. The following study visits cannot be conducted over the phone: Screening Visit (Week 99), Baseline (Week 0), Week 3, and Week 6. Additionally, phone visits may not occur for two consecutive visits.

During study visits:

- A study doctor will ask the participant questions about the participant's ASD symptoms and general health. The study doctor will also ask if the participant is having any side effects, and if they have taken any other medications during the previous week (see Table I for details).
- We will measure participant's blood pressure, heart rate, and weight. Participant's height will measured at Week 6.
- We will ask the participant to fill out seven questionnaires at Weeks 0 and 6, and five questionnaires at Week 3. This will take approximately 30-40 minutes. At Weeks 1, 2, 4, and 5, we will ask the participant to complete one questionnaire (approximately 10 minutes).
- Optional: If a parent/caregiver is available, we will ask them to complete two informant-rating scales assessing the subject's social responsiveness (SRS-2) and the subject's symptoms associated with ASD (MGH-SECS-I) at weeks 0, 3, and 6.
- At Week 6, we will ask the participant for a urine sample in order to test for prescription drugs, illegal drugs, and controlled substances (substances that may be habit-forming). For female participants of childbearing potential, we will also test for pregnancy.
- At Weeks 0 and 6, the participant will complete the following cognitive assessments: CANTAB, WAIS-IV, and DANVA 2. The total time for these assessments will be approximately 3 hours.
- During the final study visit (Week 6), we will conduct another ECG, physical exam and blood draw.

For quality control purposes, assessments completed during these visits may be recorded. These recordings will be used to monitor quality control and inter-rater reliability in this study. Each recording will be coded with subject initials and an identification number to maintain confidentiality. These recordings will be stored in a password-protected database or on an encrypted external hard drive stored in a locked filing cabinet in a secure office.

Study Discontinuation

A participant may withdraw consent at any time for any reason (e.g., lack of efficacy, adverse events, etc.). A subject may be withdrawn from the study at any time if any of the following conditions are met:

- Worsening of ASD, ADHD, anxiety, depression, mania, OCD or psychosis, as determined per clinician judgment informed by a comprehensive review of subjects' initial psychiatric evaluation chart notes and progress notes from prior study visits as well as current clinical assessment.
- Subjects who experience intolerable adverse effects, and/or clinically significant laboratory values inconsistent with continuation in the study as determined by the PI.
- Unstable psychiatric condition that clinically requires 1) treatment with prohibited concomitant psychotropic medications or 2) subjects requiring inpatient psychiatric admission.
- Emergent suicidality

- Active substance abuse
- Pregnancy
- Allergic drug reaction
- Non-compliance (less than 70% compliance for 2 visits or longer)
- Failure to return medication for 2 consecutive visits
- Failure to keep study appointments for more than 2 consecutive visits without justification
- Clinical judgment of the investigator

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 may receive three clinical follow-up visits at the completion of the study (or if they are required to discontinue for safety reasons), allowing adequate time for appropriate psychiatric referrals to treaters in their communities. Follow-up visits are optional and are at no cost to participants. These visits are not part of the clinical trial and no research data will be collected during follow-up. Subjects who fail to return medication for two consecutive visits, fail to keep study appointments, or are non-compliant (less than 70% compliance for two weeks or longer) may be dropped from the study. These study subjects will be given a referral to treaters in their area but will not be offered three follow-up visits.

If a subject would like us to forward their clinical history to his/her primary care physician, or a new clinician, we will forward any pertinent information with the proper completed release of information authorization form. If a subject who has come from the clinic of the investigator happens to drop out of the study, he or she will return to his or her treating physician.

8. ASSESSMENTS (See Table I for an assessment schedule)
Given the pharmacokinetics and pharmacodynamics of MPH, subjects will be evaluated at weekly intervals. At each weekly visit, measures of safety and efficacy will be obtained using assessments of psychiatric symptoms and functioning (AISRS, CGIs, GAF), measures of adverse effects (CTAE), and vital signs. At the midpoint (Week 3) and final study visits (Week 6), additional clinician- and subject-rated assessments will be repeated (see below for details).

Diagnostic Assessments
(Administered at screening evaluation)

- Structured Diagnostic Interview: The Kiddie-Schedule for Affective Disorders and Schizophrenia-Epidemiologic Version (K-SADS-E; Orvaschel 1994) is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in youth according to DSM criteria. Probes and objective criteria are provided to rate individual symptoms. It provides a standardized method of obtaining and recording symptoms necessary for the assessment of diagnostic categories. It can be effectively administered by clinicians or trained interviewers.

We will also collect ages of onset and offset for each disorder. The ADHD module of K-SADS-E will be administered in this trial for confirming the diagnosis of ADHD.

- Autism Diagnostic Observation Schedule (ADOS; Lord et al.,1994): The ADOS is an instrument that allows diagnosis and assessment of autism across age, developmental level, and language skills. The assessment consists of a series of semi-structured tasks that involve social interaction between certified rater and subject.
- MGH Autism Spectrum Disorder DSM-5 Diagnostic Symptom Checklist (MGH-ASD-SCL): The range and severity of subjects' ASD symptoms will be assessed with the clinician-administered MGH-ASD-SCL. This screening instrument adopted items from DSM-5 diagnostic criteria for ASD and assesses for the individual core domains and associated features of ASD.

Cognitive Assessments

(Administered at screening evaluation)

- Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II; Wechsler, 2011): *Vocabulary* and *Matrix* subtests will be administered. This scale meets the demand for a quick reliable measure of intelligence and determines verbal, performance, and full-scale IQ scores.
- Wechsler Adult Intelligence Scale (WAIS-IV; Wechsler 2008): *Digit Span*, *Arithmetic*, and *Letter/Number Sequencing* subtests will be administered to assess working memory; *Digit/Symbol Coding* and *Symbol Search* subtests will be administered to assess processing speed.

(Administered at baseline and final study visit)

- Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition Limited, 2004): The CANTAB is designed to assess executive functioning. The subtests we use are not sensitive to practice effects. Subtests will include the following:

-Working Memory and Planning:
-*Spatial Working Memory (SWM):* tests comprehension, learning, and reversal.
-*Stockings of Cambridge (SOC):* assesses spatial planning and motor control.
-Attention
-*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.
-Response Control
-*Affective Go/No-Go (AGN):* assesses information processing biases for positive and negative stimuli.
-Verbal Memory

-*Verbal Recognition Memory (VRM):* assesses immediate free recall, and immediate and delayed recognition memory.

- Diagnostic Analysis of Nonverbal Accuracy Scale (DANVA2; Nowicki & Carton, 1993): The DANVA 2 consists of tasks of social competence, testing subjects' ability to recognize feelings expressed through faces and paralanguage by adults and children. Child and Adult Facial Expressions subtests are used to assess face-emotion labeling. Each computer-administered subtest includes 24 photographs of child or adult models (12 female, 12 male per subtest) displaying equal numbers of high- and low-intensity expressions of happiness, sadness, anger, and fear. Faces appear for 2 seconds. In a forced-choice format, participants indicate by button-press which emotion a face expresses. Both subtests have been standardized and have acceptable internal consistency and reliability (Nowicki & Carton, 1993; Constantino et al., 2000). Participants will complete *Adult Faces* and *Adult Paralanguage* subtests.

Clinician-Rated Behavioral Measures

(Administered at baseline, weekly study visits, midpoint, and endpoint)

- Adult ADHD Investigator Symptom Report Scale (AISRS; Spencer et al., 2010): The AISRS, shown to be sensitive to drug effects in adult populations, assesses each of the 18 individual criteria symptoms of ADHD in DSM-IV on a severity grid (0=not present; 3=severe; overall minimum score=0; maximum score=54).
- Clinical Global Impression Scale (CGI; National Institute of Mental Health, 1985): The CGI is a measure of illness severity, improvement, and efficacy of treatment. The score for severity ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill subjects). Improvement ranges from 1 (very much improved) to 7 (very much worse). The effectiveness index measures to what extent the subject is experiencing therapeutic effects in conjunction with the level of adverse events they are experiencing. CGI scales will be used for the assessment of *ADHD* and *ASD*.
- Global Assessment of Functioning Scale (GAF; Endicott et al., 1976): composite rating of an individual's overall level of functioning (1= worst to 100 = best).

(Administered at baseline, midpoint, and final study visits)

- MGH Social-Emotional Competence Scale [Clinician-Rated Measure] (MGH-SECS-C): This is a 37-item scale that assesses change in the frequency and severity of core and associated symptoms of ASD.
- Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al., 1989): This is a clinician-rated 10-item scale (total range from 0 to 40), with subtotals for obsessions (items 1-5) and compulsions (items 6-10). The Y-BOCS has been shown to be both a reliable and valid measure of OCD symptomatology in adults as well as responsive to changes with treatment.
- Hamilton Anxiety Scale (HAM-A; Hamilton, 1959): a rating scale used to assess anxiety. This questionnaire consists of 14 questions assessing these symptoms. Clinicians are asked to rate each symptom as absent, mild, moderate, severe, or very severe.
- Hamilton Depression

- Young Mania Rating Scale (YMRS; Young et al., 1978): is an 11-item interview that queries the core symptoms of mania, including elevated mood, irritability, psychomotor agitation, hypersexuality, and aggressive behavior. The YMRS score ranges from 0-60 and asks about symptoms of the previous week.
- Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1988): a scale commonly used to assess overall psychopathology. The scale consists of 18 items, each rated on a scale from 1 (symptom not present) to 7 (symptom extremely severe).

Subject-Rated Behavioral Measures

(Administered at screening evaluation)

- Demographic Interview: This brief interview will collect information regarding socioeconomic status and history of head injury or trauma (Hollingshead, 1975).
- Social Responsiveness Scale-Second Edition Self-Report (SRS-2; Constantino & Gruber, 2012): a 65-item rating scale completed by subjects that is used to measure the severity of autism spectrum symptoms as they occur in natural settings.

(Administered at baseline, weekly study visits, midpoint, and endpoint)

- Adult ADHD Self-Report Scale (ASRS; Adler et al., 2006): The 18-item ADHD Rating Scale will be completed to evaluate frequency of ADHD symptoms on a scale of 0 to 4.

(Administered at baseline, midpoint, and final study visits)

- Social Responsiveness Scale-Second Edition Self-Report (SRS-2; Constantino & Gruber, 2012): a 65-item rating scale completed by subjects that is used to measure the severity of autism spectrum symptoms as they occur in natural settings.
- Behavior Rating Inventory of Executive Function-Adult Self-Report Version (BRIEF-A; Roth, Isquith, & Gioia, 2004): a 78-item rating scale to assess level of executive function deficits.
- Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott, Nee et al. 1993): a 16-item questionnaire to evaluate the degree of enjoyment and satisfaction experienced in eight areas of daily functioning.
- Social Responsiveness Scale-Second Edition Informant-Report (SRS-2; Constantino & Gruber, 2012): a 65-item rating scale completed by parents/caregivers that is used to measure the severity of autism spectrum symptoms of the subjects as they occur in natural settings.
- MGH Social-Emotional Competence Scale [Informant-Rated Measure] (MGH-SECS-I): This is a 37-item scale that assesses change in the frequency and severity of core and associated symptoms of ASD.

(Administered at baseline and final study visits)

- Social Adjustment Scale (SAS; Weissman and Bothwell 1976): a 54-item multiple-choice questionnaire to assess social functioning.
- Driver Behavior Questionnaire (DBQ; Reason et al, 1990): A 24-item scale to assess driving behaviors and frequency of driving errors and violations.

Clinician-Rated Safety Measures
(Administered at baseline, weekly study visits, midpoint, and endpoint)

- Clinician-Rated Treatment Emergent Adverse Events Log (CTAE): to record any spontaneous adverse health events experienced during the study, along with duration, severity, cause, treatment, and outcome.
- Concomitant Medications: to record additional medications taken during the study.

9. DATA ANALYSIS

Statistical Analysis

Considering the open-label single group design, we will rely on comparisons of the participants' performances at baseline prior to the initiation of treatment relative to their scores at the last assessment (completion/drop-visit). Thus, statistics for paired samples will be utilized. This design largely protects against the bias introduced by confounding factors. That is, since the same participants are tested on two occasions, all static confounding factors are perfectly balanced, and can have no impact on the findings. Bias can still result from time-varying factors that are not associated with the outcomes, but we are confident that any such factors will have a minimal impact on this study considering the duration of the trial. Specifically, we will employ Wilcoxon signed rank tests for continuous or discrete outcome measures, and McNemar's test for binary outcomes. These tests are free from assumptions regarding the distribution of the outcome variables, which is appropriate since the scales we are proposing to utilize are not considered to have Gaussian distributions, and will not be amenable to parametric methods.

10. SAFETY

Consistent with good clinical practice, safety will be monitored at each study visit by a subject's assigned clinician. This clinician will be available 24 hours a day by page. The principal investigator will supervise all study activities including ratings, reported adverse events, laboratory tests, and vital signs. All procedures have been designed to minimize subject discomfort, and no subject will be asked to engage in research procedures not outlined in the consent form.

If a subject is withdrawn from the study due to adverse events, lack of response, or as a decision by the clinician, they will be offered open treatment for three months, giving adequate time for appropriate psychiatric care to be arranged.

Blood Draw

A topical anesthetic cream (EMLA) will be offered to subjects before blood draws. The dose of EMLA cream will not exceed administration guidelines based on subject age and weight. Subjects with sensitivity to local topical anesthetics will not receive EMLA cream. If an infection does occur, it will be treated.

Study Medication

Safety will be monitored through treatment-emergent adverse events and measuring change in vital signs through laboratory analyses. Subjects will be monitored for adverse events at each visit. All adverse events will be recorded. A subject may be dropped from the study or dosage may be decreased and timing of medication changed at any time due to adverse events. All adverse events will be reported to the PHRC according to PHRC guidelines. All concomitant medications will be assessed at every study visit. At screening, subjects with contraindicated concomitant medications will be given the option of discontinuing such medications (see Washout Period, pg. 10) or will be withdrawn from the study.

11. 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. While the results of the clinical laboratory blood testing will become part of a subject's Massachusetts General Hospital medical record, they will not link the subject to participation in any research. 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.

12. RISKS AND DISCOMFORTS

Frequent Adverse Events Related to Study Drug
Methylphenidate hydrochloride for extended-release oral suspension (Quillivant XR) is a central nervous system (CNS) stimulant indicated for the treatment of attention-deficit/hyperactivity disorder. Based on accumulated data from other methylphenidate products and limited clinical trial data on Quillivant XR in children with ADHD, common adverse reactions (≥2% and twice the rate of placebo) are decrease in appetite, weight loss, nausea, abdominal pain, dyspepsia, dry mouth, vomiting, insomnia, anxiety, nervousness, restlessness, affect lability, agitation, irritability, dizziness, vertigo, blurred vision, increase in blood pressure, tachycardia, increased sweating, fever, excoriation, tics, motion sickness, eye pain, and rash.

Heart-related problems including sudden death, stroke, and myocardial infarction have been reported with use of MPH and other stimulant medications. CNS stimulants may exacerbate behavior disturbance or thought disorder in patients with a pre-existing psychotic disorder, may induce a manic or mixed episode in patients with bipolar disorder, and may induce manic or psychotic symptoms in patients without a prior history of mania/psychosis. There have been reports of priapism and peripheral vasculopathy, including Raynaud's phenomenon, in association with MPH treatment. MPH is a federally controlled substance with high potential for abuse and dependence.

All participants will be closely monitored for serious adverse reactions. All serious unexpected adverse events will be reported to the sponsor (Pfizer, Inc.) and the Partners Human Research Committee as stipulated by Pfizer and PHRC regulations.

Other Adverse Events Related to Study Drug
Problems and side effects not listed above and not known at this time could occur. Subjects will be informed of any newly discovered risks as investigators come to learn of such knowledge, if applicable.

Risks of Blood Draws
When blood is drawn, some discomfort may occur. Bruising and/or bleeding at the needle site may occur. Occasionally a person feels faint. Rarely, an infection may develop. If an infection does occur, it can be treated. A topical anesthetic cream (EMLA) will be offered to subjects to numb the skin where blood will be drawn if subjects prefer.

Risks of Assessments/Questionnaires
Some questions may make subjects feel uncomfortable because of the nature of the question topics. Some questions ask about possibly sensitive information, including questions pertaining to alcohol and drug abuse. Subjects may refuse to respond to any questions they do not feel comfortable answering.

Adverse events and unanticipated problems will be reported to the PHRC according to current guidelines. We will follow and adhere to all guidelines as defined and outlined on the Partners Human Research Committee web site: (http://healthcare.partners.org/phsirb/adverse_events.htm).

13. POTENTIAL BENEFITS

There may be no direct benefit to subjects participating in this study. Participants may benefit by potentially experiencing improvement in ADHD symptoms and by gaining knowledge about ASD and ADHD.

Table I. Study Schema

Visits (Weeks)	**99**	**0**	**1**	**2**	**3**	**4**	**5**	**6**
MPH-ERLF Dose Titration (mg/per day)		5	20	50	60*	60*	60*	60*
Informed Consent	X							
Diagnostic Assessments								
MGH-ASD-SCL	X							
Psychiatric Evaluation & Medical History	X							
ADOS	X							
K-SADS-E ADHD Module	X							
Physiological Procedures								
Physical Examination	X							X
Urine pregnancy test (females only)	X							X
Urine drug screen	X							X
Hematological tests	X							X
EKG	X							X
Vital Signs (pulse, BP & weight)	X	X	X	X	X	X	X	X
Height	X							X
Cognitive Assessments								
IQ Assessment (WASI)	X							
CANTAB, WAIS-IV, DANVA2		X						X
Clinician-Rated Assessments								
AISRS	X	X	X	X	X	X	X	X
MGH-SECS-C		X			X			X
CGI-ASD	X	X	X	X	X	X	X	X
CGI-ADHD	X	X	X	X	X	X	X	X
Y-BOCS		X			X			X
HAM-A		X			X			X
HAM-D		X			X			X
YMRS		X			X			X
BPRS		X			X			X
GAF		X	X	X	X	X	X	X
CTAE		X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Patient-Rated Assessments								
Demographic Interview	X							
ASRS		X	X	X	X	X	X	X
SRS-2 (Self)	X	X			X			X
BRIEF-A		X			X			X
SAS		X						X
DBQ		X						X
Q-LES-Q		X			X			X
Informant-Rated Assessments								
SRS-2 (Informant)		X			X			X
MGH-SECS-I		X			X			X

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