



## **HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)**

### **Protocol Title:**

*Effects of Evening Dose of Immediate Release CNS Stimulants on Sleep in Children with Attention Deficit Hyperactivity Disorder: A Randomized Placebo-controlled Pilot Study*

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## 1.0 Objectives

### 1.1 Study Objectives

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common reasons for child mental health referrals in children affecting over 11% of school-aged youth at an annual societal cost of over 40 billion dollars. Similar to ADHD, pediatric sleep disorders are a significant public health problem as they occur in over a third of children and impact multiple domains of the child's functioning as well as that of their parents. Children with ADHD are at an increased risk for sleep problems with a staggering comorbidity of up to 70%, while sleep deprivation worsens the already impaired social, emotional and academic functioning of children with ADHD. Therefore, improving sleep may translate into enhanced functioning in multiple realms. Delayed sleep onset latency (SOL) and bedtime resistance, the key component of the limit setting type of Behavioral Insomnia of Childhood (BIC), are particularly likely to occur in children with ADHD. Oppositional behaviors have been identified as major causes of these sleep problems in ADHD youth. Medications are commonly used for both conditions with over 6% of all school-aged children in the United States prescribed medication for ADHD and 7% for sleep. In children with ADHD, 34% of prescribed sleep medications are antipsychotics that can cause marked weight gain and metabolic changes. Alternate medications for sleep have either been found to be ineffective, difficult to tolerate or are largely unstudied in youth.

Methylphenidate (MPH marketed as Ritalin) and Amphetamine (AMPH marketed as Adderall) are the two most commonly prescribed CNS stimulant medications for ADHD and they have an extensive database supporting their safety and efficacy. While insomnia is a commonly reported side effect of this medication class, objective sleep studies of either have not found consistent results, with a few studies reporting delayed SOL and while others report improved quality of sleep. For example, one study found the switching from BID to TID dosing schedules of immediate release MPH (IR MPH) actually led to reductions in SOL by 25%. Past studies have been limited by their setting (inpatient and sleep labs), sample (large percentage of treatment naïve patients), design (open label), and assessment methods (heavy reliance on parental report). A major limitation has been the failure to disentangle the direct effects of MPH and AMPH from that of the exacerbation of ADHD symptoms due to the waning of the therapeutic effects of a morning dose of a CNS stimulant (medication rebound). Unfortunately, this process occurs during the midst of the bedtime routine for many school aged children treated with CNS stimulants, which may lead to worsening in SOL due to increased behavioral problems as children are supposed to be calming down for bedtime. Hence, there is a clear need for alternate treatments option for frequently occurring sleep problems in school-aged children with ADHD.

We propose to address the aforementioned limitations through objective measures by using a double blind with-in subjects design. We also propose to evaluate the impact of extending CNS stimulant treatment into the early evening on sleep onset in school-aged youth, who have been diagnosed with ADHD and currently use MPH or AMPH, to determine if the extension of MPH or AMPH is effective in eliminating or lessening interruptions during the bedtime routine. In addition, this proposal will gather the essential preliminary data needed to support a K23 application on multimodal interventions for sleep problems in children with ADHD as our center is also developing a novel behavioral treatment that targets both sleep hygiene and externalizing behavior symptoms. Our objectives for this study are to:

**Aim:** In 38 children already stabilized on a regimen of AMPH or MPH who have chronically delayed sleep onset latency, we propose to assess the impact of extending CNS stimulant treatment into the evening on sleep during a 3-week, with-in subjects randomized trial. Participants stable on MPH will be given a 0.3mg/kg dose of IR MPH or placebo between administered in the early evening. Those already taking a stable dose of AMPH will be given a 0.15mg/kg dose of IR AMPH or placebo in the later afternoon.

**H1:** We expect that the Immediate Release CNS stimulants (IR MPH or IR AMPH) will produce a significant reduction in evening levels of ADHD/ODD symptoms compared to placebo,

- H2: Sleep latency will be significantly shorter on days with IR MPH/AMPH vs placebo  
 H3: Improvement in evening symptoms of ADHD/ODD will be correlated with change in sleep latency.

### 1.2 Primary Study Endpoints

The primary outcome in this study will be the duration of time in bed until sleep measured in minutes (Sleep onset latency; SOL) as reported on the parent completed sleep log. Sleep logs are the most reliable means for assessing SOL.<sup>6, 13, 31</sup> Parents will complete the paper sleep log every 15 minutes starting with the first request to go to bed until the child is asleep for two intervals.

### 1.3 Secondary Study Endpoints

Sleep onset latency (SOL), defined as time in bed until sleep, will be measured by sleep log vs. actigraphy as sleep logs are commonly used in ADHD sleep studies and because SOL is the least reliable sleep parameter on actigraphy.<sup>6,13,31</sup> Parents will complete the paper sleep log every 15 minutes starting with the first request to go to bed until the child is asleep for two intervals, and record the time first in bed. In the morning, they will record nighttime wakings, morning wake time and the time the child arises from bed to calculate total time in bed. As recommended, actigraphy and sleep logs will both be used to enhance data quality and obtain objective and subjective markers of habitual sleep patterns.<sup>32</sup> Participants will wear the GT3X ActiGraph (Pensacola, FL) on their non-dominant hand for two weeks at baseline, during study period (3 weeks) from 30 minutes before bedtime to 30 minutes after morning rising, set at 30Hz using 1 minute epochs. Besides sleep onset and SOL, actigraphy will measure sleep offset, total sleep time, wake after sleep onset (WASO), sleep efficiency, number and length of wakings and night to night variability (weekends & weekdays). The parent rated 10-item IOWA Conners will assess change in ADHD and ODD symptoms specifically during the time periods between 6pm to bed time.<sup>33</sup> The parents rated 7-item the Affective Reactivity Index (ARI) will assess change in irritability.<sup>42</sup> All scales have been found to be reliable markers of treatment response.<sup>25</sup> We will use the Pittsburgh Side Effects Rating Scale (PSERS) to evaluate adverse reactions to MPH and AMPH.<sup>34</sup> The PSERS lists common stimulant induced adverse events rated none too severe. It was used in the MTA and other stimulant trials.<sup>35,36</sup> As side effects and ADHD/ODD symptoms will be completed nightly during these 3 weeks of treatment, we elected to use these brief measures. These brief measures have been found to be as sensitive for detecting treatment effects of CNS stimulants compared to lengthier measures that assess the entire range of DSM externalizing symptoms.<sup>25</sup>

## 2.0 Background

### 2.1 Scientific Background and Gaps

Children with ADHD have more sleep disturbances than those without ADHD, irrespective of their medication status.<sup>1</sup> Behavioral Insomnia of Childhood (BIC) is the most common sleep disorder seen in youth with ADHD with delayed sleep onset latency (SOL) being the primary manifestation of BIC.<sup>2</sup> Rates of BIC exceed in children with ADHD those seen in children with mood and anxiety disorders.<sup>3</sup> Contributing factors to a prolonged SOL in children with ADHD include poorly structured night time routines, highly variable bedtimes and elevated levels of bedtime resistance.<sup>4,5</sup> Sleep deprivation has been also linked with oppositional behavior and irritability<sup>6,43</sup>. Sleep experts have concluded that oppositional behaviors likely drive the majority of sleep problems in children with ADHD, suggesting that helping parents to manage these behaviors may improve the child's sleep.<sup>6,7</sup>

Behavioral interventions for sleep problems may be more difficult to implement in youth with ADHD and there is very little data on the behavioral treatment of sleep in youth with ADHD.<sup>2</sup> Not surprisingly, medications are the most common intervention for sleep problems in youth with ADHD. Most medications for sleep have been found to be ineffective, or are largely unstudied in youth.<sup>8</sup> In children with ADHD, 34% of prescribed sleep medications are antipsychotics.<sup>1</sup> However, the use of antipsychotic medication in ADHD youth without serious psychiatric comorbidity is difficult to recommend given the concerning side effect profiles of these medications,<sup>9</sup> their limited efficacy for ADHD<sup>10,11</sup> and increased

concerns over polypharmacy in children.<sup>12</sup> Melatonin has been proven efficacious under controlled settings but does not impact ADHD symptoms and most responders still exhibit prolonged sleep latencies.<sup>13</sup> Hence, there is a clear need for additional treatment options.

## 2.2 Previous Data

N/A

## 2.3 Study Rationale

CNS stimulant medications have an extensive database supporting their safety and efficacy in children, but there is a strong perception among parents and clinicians that stimulant can worsen sleep problems based on their wakefulness promoting properties.<sup>14</sup> Objective sleep studies measuring effects of MPH have not found consistent results. Stimulant regimens designed to control symptoms during the school lose efficacy as bedtime approaches, leading to worsening behavior in the early evening.<sup>15</sup> Rebound ADHD symptoms when children are trying to settle for bedtime have been theorized to prolong SOL.<sup>7,16,17</sup> Therefore, extending the effects of CNS stimulants may lead to improved SOL through reduction of disruptive behaviors in the evening.

In treatment naïve youth, afternoon doses of IR MPH worsen SOL.<sup>18</sup> However, many side effects of CNS stimulants fade over time.<sup>19</sup> Therefore, results in treatment naïve youth may not translate to chronically treated youth. In fact, later day dosing of CNS stimulants has been found to improve sleep in children and adults with ADHD.<sup>16</sup> Stein et al. found that SOL was reduced by 25% when the therapeutic effects of CNS stimulants were extended into the early evening by adding a third dose of IR MPH in a double blind controlled trial in children already optimized on a IR MPH regimen.<sup>20</sup> The last dose in the TID regimen was at 4pm which may not have prevented a symptom exacerbation during the bedtime routine for some participants, possibly blunting observed improvements in SOL. Extending the wear time of the MPH patch in children from 9 to 12 hours exerted a tendency toward improved sleep quality on subjective measures<sup>21</sup>, while MPH dosed as late as 8pm led to reductions in the frequency of night-time awakenings leading to improved sleep quality in adults.<sup>22</sup> Likewise, one study in children chronically treated with CNS stimulants found that dosing extended release amphetamine products so they carry into the evening resulted in a higher sleep efficiency compared to placebo, although did not reach to statistical significance.<sup>46</sup>

The impact of extending CNS stimulant effects into the evening on SOL has not been adequately investigated and merits further study in light of the limitations of current practices for improving sleep in children with ADHD.

## 3.0 Inclusion and Exclusion Criteria

### 3.1 Inclusion Criteria

1. Ages 6-12 (inclusive), as sleep architecture changes as children pass through puberty.<sup>23</sup>
2. Children who have been treated with a stable morning dose of Extended Release Methylphenidate or Amphetamine (ER AMPH) or twice daily dose of Immediate Release Methylphenidate or immediate release amphetamine (IR AMPH) for an extended period of time (30 days or longer).
3. DSM V diagnosis of Attention Deficit Hyperactivity Disorder (ADHD): Diagnosis will be assessed on the NIMH Computerized Diagnostic Interview Schedule for Children (C-DISC)<sup>24</sup>, and parent and teacher rating scales.<sup>25</sup> The C-DISC is a structured parent interview that is widely used in pediatric mental studies to classify diagnostic status. Computerized administration is overseen by trained study staff and the computerized diagnostic score is overseen by MD/PhD level faculty. Assessment questions for the C-DISC are not provided with this IRB submission as questions vary depending on subject responses, and a file containing the questions would be too large (100+ pages). Additionally, as evening levels of ADHD and Oppositional Defiance Disorder (ODD) symptoms are theorized to mediate improvements in sleep onset latency (SOL), scores at or above the 90th percentile on the 10 item IOWA Conners, specifically during the time period between 6:00 p.m. to bed time will be required. This cutoff represents an elevated level of disruptive symptoms for the age.<sup>26</sup>

4. Children with any ADHD subtype meeting the above criteria will be eligible, although, it is expected that the majority will be of the Combined subtype of ADHD given the association between this subtype and ODD symptoms.<sup>27</sup> A diagnosis of any of the two Behavioral Insomnia of Childhood (BIC) subtypes associated with delayed SOL (limit setting or combined type) will be required.<sup>28</sup> A SOL  $\geq 30$  minutes for the past three months by parent report and verified during a 14 day pre-baseline assessment (parent completed sleep log) will be required. In a large population-based study, average sleep onset latency was 17.2 minutes in school age children.<sup>49</sup> Additionally, widely used sleep screening instrument 'Children's sleep Habits questionnaire' in school-aged children – indicates that normal sleep onset latency should be less than 20 min.<sup>50</sup> Therefore, we feel that lowering the SOL threshold will allow more children in need of treatment to enroll without inadvertently including those with minimal impairing sleep problems. In children, SOL is typically  $\leq 20$  minutes with a SD of 15 minutes.<sup>30</sup> Further, the delayed SOL must persist once stimulant medication is stopped, which will be verified through the 14 day parent completed sleep log, with children stopping their stimulant medication on 2 of the 14 days. The unmedicated assessment days are included to document that the delayed SOL does not resolve with stoppage of the CNS stimulant. Susan Calhoun, PhD, will confirm the diagnosis of BIC through review of parent completed sleep log and parent completed sleep assessment. Dr. Calhoun has over a decade of experience in the assessment and behavior management of pediatric sleep disorders.

4. Sex: male or female
5. Fluent in written and spoken English.
6. Children who can swallow capsules.

### 3.2 Exclusion Criteria

1. Age  $< 6$  years of age or  $> 12$  years of age.
2. Children who have not had Methylphenidate or Amphetamine (Extended Release or Immediate Release) treatment for an extended period of time (30 days or longer).
3. A diagnosis or suspicion of sleep-disordered breathing will be exclusionary as it is not expected to be impacted by Immediate Release Methylphenidate treatment.
4. Current psychotropics other than CNS Stimulants (Extended Release or Immediate Release Methylphenidate or Amphetamine). Children prescribed alpha agonists for adjunctive control of ADHD in combination with a MPH product will be allowed to enroll as long as they meet all other entry criteria (i.e. sleep must remain impaired with use of alpha agonist).
5. Regular use of other medications that impact sleep within the last 14 days (i.e.: sedating antihistamines, melatonin).
6. Active medical/psychiatric conditions that impact sleep (i.e.: severe asthma, Autism Spectrum Disorder diagnosis, marked developmental delay, or mood/anxiety disorder).

### 3.3 Early Withdrawal of Subjects

#### 3.3.1 Criteria for removal from study

Participants are free to withdraw at any time from the study. The principal investigator may withdraw participants from the study at any time without patient consent for health and safety reasons, failure to adhere to protocol requirements, participant consent withdrawal, or if it is in the participant's best interest. Any participant experiencing a 50% worsening in sleep onset latency will be discontinued, and participants can be brought in for additional visits as needed to assess tolerability or efficacy concerns.

#### 3.3.2 Follow-up for withdrawn subjects

If participants withdraw or are withdrawn from the study prior to the completion of the study, they will not be replaced. Research staff will contact the participants for close up visit for assessment of safety, to collect and obtain any possible data that may be available such as partial sleep logs and/or actigraphy data.).

## 4.0 Recruitment Methods

### 4.1 Identification of subjects

Potential research participants will be recruited through mailed flyers, flyers provided within pediatric and psychiatric clinics within Hershey Medical Center, and Penn State Children's Hospital website. CareLine staff will also be provided with language in order to provide interested research participants with information about the study (supporting form included in this IRB modification submittal). CareLine will forward all interested participant information to research staff. An on-hold message through Penn State Hershey Medical Center will also be used to recruit participants.

### 4.2 Recruitment process

Participants will be recruited from pediatric and psychiatric clinics at Penn State Hershey Medical Center, as well as through mailed flyers. Recruitment efforts will also take place through the Penn State Children's Hospital website, where a link and description of the study will be included, Penn State Milton S. Hershey Medical Center Facebook page, and the Penn State Hershey Research Facebook page to display the IRB approved recruitment flyer. Interested parents will be instructed to call research staff to complete a brief screening for eligibility over the phone. Participants meeting the phone screen criteria will be invited to schedule an intake appointment at the Hershey Medical Center Psychiatry Clinic at 22 Northeast Drive.

### 4.3 Recruitment materials

See documents attached in CATS:

- recruitment flyer
- cover letter to mail with ABC Brochure and recruitment flyer
- text for CareLine document
- text for on-hold message document.
- text for Penn State Children's Hospital website document

### 4.4 Eligibility/screening of subjects

See attached phone screening form.

## 5.0 Consent Process and Documentation

### 5.1 Consent Process

#### 5.1.1 Obtaining Informed Consent

##### 5.1.1.1 Timing and Location of Consent

Consent procedures will take place at the 22 Northeast Drive, HMC Department of Psychiatry Child Research Annex and will be conducted by the principal investigator or other MD/PhD level study staff approved to collect consent. The consent visit will be scheduled after meeting screening criteria from the phone screen.

##### 5.1.1.2 Coercion or Undue Influence during Consent

The potential participant and parent will be told that the research is voluntary. The potential participant and parent will be told that the research will not impact their treatment at all, and that he or she may refuse research at any time.

**5.1.2 Waiver or alteration of the informed consent requirement**

N/A

**5.2 Consent Documentation**

**5.2.1 Written Documentation of Consent**

No research will be conducted until after consent has been obtained. After a potential participant is identified via the phone screen with the participant's guardian, the participant and guardian will be approached by a member of the research staff to discuss the consent process. The member of the research staff will inform the parent and child about the purpose of the study, the risks and benefits, and the procedures for the study. During this conversation, the member of the research staff will assess the level of insight of the parent/guardian of the patient into the illness. If the parent is unable to demonstrate adequate insight, the member of the research staff will decide that they are unable to consent at that time. If the parent is interested and eligible they will sign the consent form. Parents will be offered the opportunity to take the consent home for further review before signing, in which case the intake process will end for that day. A copy of the signed consent form will be provided to the family.

**5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)**

Verbal consent is required to complete the phone screen. PHI will be collected to determine if a potential subject has any cardiovascular conditions or a family history of cardiovascular conditions to determine study eligibility.

**5.3 Consent – Other Considerations**

**5.3.1 Non-English Speaking Subjects**

N/A

**5.3.2 Cognitively Impaired Adults**

N/A

**5.3.2.1 Capability of Providing Consent**

N/A

**5.3.2.2 Adults Unable To Consent**

N/A

**5.3.2.3 Assent of Adults Unable to Consent**

N/A

**5.3.3 Subjects who are not yet adults (infants, children, teenagers)**

**5.3.3.1 Parental Permission**

Designated members of the research team will meet with the parent or legal guardian to review the consent document in a private area and then answer all questions regarding to the study. Consent will be provided via a signature area labeled "Signature of Parent(s)/Guardian for Child". Legal guardians will be requested to provide documentation of their guardianship.

**5.3.3.2 Assent of subjects who are not yet adults**

All participating children will be between 6 and 12 years of age. Study doctors will review the study with the potential participant as well as their legal guardian in a private area. Once the assenting clinician has verified that the child has an age appropriate understanding of the study and is willing to participate, the child will



then sign the consent form under the section assent for research participant ages 7 and up. Due to their level of cognitive maturity or severity of behavioral symptoms (as this study targets child with attention and/or oppositional behaviors), some children may not be able to express sufficient understanding of the study. In such cases, the assenting clinician will verify with the parent that the child will be a willing and appropriate participant but that their behavioral symptoms prevent them from signing assent. In such cases, the need for child signature will be waived and the consenting clinician will document the reason the child's signature was not obtained.

## 6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

### 6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

- ☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*
- ☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*
- ☐ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*
- ☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*
- ☒ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

### 6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

#### 6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

##### 6.2.1.1 Plan to protect PHI from improper use or disclosure

Each participant will be assigned a unique study ID code. The only identifying information on any study form will be that ID code. PHI will not be recorded on any study assessment form other than the phone screen and consent form. These two forms will be kept in separate locked file apart from the rest of the study data for individual participants. The only database linking study ID number to PHI will be stored on a secure departmental server accessible only to core study staff.

##### 6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

No PHI will be encoded on study forms. Participants' phone screens that contain PHI will be kept in a secure locked area within the research site to ensure that we have a means to contact families if needed.

#### 6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

This is a study of the effects of Immediate Release Methylphenidate on ADHD in children, which requires examination of individual participants.

**6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization**

PHI will be collected over the phone via phone screen. This requires a waiver of authorization statements of agreement because it is necessary to determine that a potential child subject does not have any cardiovascular or other medical or psychiatric conditions, which would deem them as ineligible. The phone screen will also verify that the child has been on a stable dose of an eligible ADHD medication for the required time. By collecting this information in advance, we can minimize burden to families by identifying those who are clearly ineligible prior to the lengthy consent and assessment visit.

**6.3 Waiver or alteration of authorization statements of agreement**

PHI will be collected over the phone via phone screen. This requires a waiver of authorization statements of agreement because it is necessary to determine that a potential child subject does not have any cardiovascular conditions or a family history of cardiovascular conditions, which would deem them as ineligible.

## **7.0 Study Design and Procedures**

**7.1 Study Design**

This is a double blind with-in subjects designed trial. The initial visit will be for consent and eligibility determination (Visit 1). Our core intervention will consist of 3-week with-in subjects randomized trial of adding a 0.3mg/kg of Immediate Release (IR) Methylphenidate (MPH) dosed 3 hours before bedtime vs. placebo (Visits 2-4).

**7.2 Study Procedures**

**7.2.1 Visit 1 (Intake, 2 weeks):**

Participation will involve an approximately two hour intake appointment where the participating child and legal guardian will be introduced to the study, and be consented and assented. The legal guardian will complete a standard set of clinical diagnostic interviews to assess pediatric psychopathology, as well as rating scales of the child's behavior and sleep habits. Parents will be also provided rating scales for child's teacher to complete and a record release form to obtain teacher data. Participant vitals (height, weight, blood pressure, and pulse) will be obtained. After the intake appointment, parents will be provided with a brief sleep log to record this child's time in bed, time to sleep, as well as wake time for the next 14 days. For two of these 14 days, it will be required that the child not take their normal morning dose of extended release of methylphenidate or amphetamine to ensure that the delayed sleep onset is not caused by the methylphenidate/amphetamine. Parents will select which two days are best suited for the child to minimize the impact of a potential increase in ADHD symptoms. SOL (time in bed until sleep onset) will be measured by sleep log vs. actigraphy as sleep logs are commonly used in ADHD sleep studies and because SOL is the least reliable sleep parameter on actigraphy.<sup>6,13,31</sup> Parents will complete the paper sleep log every 15 minutes starting with the first request to go to bed until the child is asleep for two intervals, and record the time first in bed. In the morning, they will record nighttime wakings, morning wake time and the time the child arises from bed to calculate total time in bed. As recommended, actigraphy and sleep logs will both be used to enhance data quality and obtain objective and subjective markers of habitual sleep patterns.<sup>32</sup> Participants will wear the GT3X ActiGraph (Pensacola, FL) on their non-dominant hand for two weeks at intake, during study period (3 weeks) from 30 minutes before bedtime to 30 minutes after morning rising, set at 30Hz using 1 minute epochs. Besides sleep onset and SOL, actigraphy will measure sleep offset, total sleep time, wake after sleep onset (WASO), sleep efficiency, number and length of wakings and night to night variability (weekends & weekdays). These parameters will be used to assess eligibility for the study, as we only want to enroll children who have a current and persistent delay in SOL. It should take parents 5 minutes or less to complete the sleep log each day. Sleep logs will be reviewed by Susan

Calhoun, PhD, who has over a decade of experience in the assessment and behavioral treatment of pediatric sleep disorders. She will also assess for the presence of any exclusionary sleep disorders using the parent completed Pediatric Sleep Questionnaire.<sup>29</sup> Participants will not be enrolled until after Dr. Calhoun has confirmed the presence of SOL on the 14 day intake sleep log. The C-DISC will be used to confirm the presence of a DSM IV disruptive behavioral disorder (DBD), assess psychiatric comorbidity with diagnoses confirmed by an MD/PhD prior to decisions on eligibility. Subthreshold mood and anxiety symptoms will be assessed as a covariate vs. being exclusionary as they are commonly seen in youth with BIC.

Sleep logs will be reviewed by phone prior to scheduling visit 2 to determine eligibility. Once all data to determine eligibility are collected, eligibility will be determined and parents of eligible participants will be asked to participate in the three weeks of IR MPH treatment.

### **7.2.2 Visit 2 (Baseline):**

The screening sleep log will be reviewed to confirm persistently delayed SOL on or off ADHD medication. Participants will be evaluated by study physicians. Participants who are already taking a stable dose of MPH will be treated with blinded IR MPH (max dose 0.3mg/kg up to a maximum of 20mg) and placebo dosed between 3 to 3.5 hours prior to bedtime over a three week period with dose (identified IR MPH dose or placebo) randomly assigned for each day. As the therapeutic effect of IR MPH lasts at least 4 hours,<sup>38</sup> and that for IR AMPH at least four hours<sup>47</sup> this dosing time should ensure that ADHD/ODD symptoms are not increasing in the midst of the bedtime routine. All children will continue on their current morning dose of an Extended Release (ER) Methylphenidate (MPH). For children whose current daytime MPH regimen is less than equivalent of 0.3mg/kg/day of IR MPH, their evening dose will be matched to their daytime dose rounded to the nearest 2.5mg increment (e.g., Concerta 18mg = IR MPH 5mg TID). No participant will receive an evening dose higher than 0.3mg/kg. For children stable on a IR or ER AMPH regimen, they will be treated with blinded IR AMPH (0.15mg/kg up to a maximum dose of 10mg) and placebo dosed 4.5 to 5 hours prior to bedtime over a three-week period with dose alternating daily given the greater therapeutic duration and potency of IR AMPH vs MPH<sup>45, 48</sup> AMPH has a longer therapeutic half-life and is twice as potent as MPH which is why the timing and mg/kg/dose is adjusted<sup>48</sup>. Participants will continue on their current dose of morning ER AMPH. For children whose current daily dose is less than 0.15mg/kg/day of IR AMPH, their evening dose will be matched to their current daytime dose (e.g. Adderall XR 10mg or Vyvanse 30mg = IR AMPH 5mg). The maximum dose of IR AMPH given will be 10mg.

A 21 day supply of blinded medication/matching placebo will be dispensed at the visit in weekly pill reminders with each day labeled. To help ensure reliable dosing, parents will have the option of daily dosing reminder by text message from study staff. Similar proceeds have been used in studies of chronic medical disease in children and found to improve administration of medication at the optimal time.<sup>39</sup> Text messages will be generated and scheduled to send to the child's parent's cell phone at a set time through Microsoft Outlook on the HMC server from a study staff's HMC email. The set time will be 3 to 3.5 hours prior to the child's bedtime as determined by the child's parent(s). The reminder message will read as follows: "This is a reminder to administer your child's study medication at X:XX p.m. today". A delivery receipt will be requested in the generation of the email to ensure deliverance of the text. Study staff will regularly check email to ensure the delivery occurred. Regular text message rates and charges will apply as per the family's mobile phone plan. Families will not be reimbursed for any incurred costs related to the reminder text messages. To verify time of dosing, parents will be asked to record time when they will give the evening dose of MPH/AMPH /placebo rounded to the nearest 5 min interval on the sleep log. Parents will complete the IOWA Conners ADHD

Rating Scale, Sleep Logs, the Affective Reactivity Index, Inattention Rating Scale, and the Pittsburgh Side Effects Rating Scale (PSERS). The parent rated 10 item IOWA Conners will assess change in ADHD and ODD symptoms specifically during the time periods between 6:00 p.m. to bed time.<sup>33</sup> The parents rated 7-item the Affective Reactivity Index will assess change in irritability<sup>44</sup>. All scales have been found to be reliable markers of treatment response.<sup>25</sup> We will use the Pittsburgh Side Effects Rating Scale (PSERS) to evaluate adverse reactions to MPH/AMPH.<sup>3</sup> If necessary, participants vitals will be obtained. For example, if vitals were not collected at visit 1, or if a significant amount of time has lapsed between visit 1 and 2 (four weeks or more). Participants will continue to wear the GT3X ActiGraph (Pensacola, FL) on their non-dominant hand from 30 minutes before bedtime to 30 minutes after morning rising, set at 30Hz using 1 minute epochs. Sleep log and actigraphy data will be collected.

#### **7.2.3 Visit 3 (3-14 days after administration of medication):**

Participant vitals will be obtained and participants will be evaluated by study physicians. Study physicians will ensure that the participant's SOL is not markedly worsened by study medication by reviewing the parent reported sleep log. Any child experiencing a 50% worsening in SOL will be either prescribed a lower dose of MPH/AMPH (decrease by at least a 2.5mg increment) or discontinued. Dose may be lowered to address other side effect concerns. Participants will continue to be treated with blinded IR MPH/AMPH (at the same dose dispensed at visit 2 unless there is a side effect concern) and placebo dosed 3 to 3.5 hours prior to bedtime. All children will continue on their pre-study morning dose of an Extended Release (ER) Methylphenidate (MPH) or Amphetamine (AMPH). To verify time of dosing, parents will be asked to record time when they will give the evening dose of MPH/placebo rounded to the nearest 5 min interval on the sleep log. Parents will complete the IOWA Conners ADHD Rating Scale, Sleep Logs, the Affective Reactivity Index, Inattention Rating Scale, and the Pittsburgh Side Effects Rating Scale (PSERS). Participants will continue to wear the GT3X ActiGraph (Pensacola, FL) on their non-dominant hand from 30 minutes before bedtime to 30 minutes after morning rising, set at 30Hz using 1 minute epochs. Sleep log data will be collected.

#### **7.2.4 Visit 4 (Endpoint):**

Participant vitals will be obtained and participants will be evaluated by study physicians. Parents will complete the IOWA Conners ADHD Rating Scale, Sleep Logs, the Affective Reactivity Index, Inattention Rating Scale, and the Pittsburgh Side Effects Rating Scale (PSERS). Sleep log and actigraphy data will be collected. GT3X ActiGraph (Pensacola, FL) will also be collected. IR MPH vs. placebo will not be administered. No treatment will be applied at this visit.

### **7.3 Duration of Participation**

Participation in the study will last approximately five to seven weeks, which includes the 2 week intake assessment and 3 study visits.

### **7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))**

#### **7.4.1 Description**

This primary aim of this study is to evaluate if variations in dosing patterns lead to better symptom control for ADHD that impacts evening behavior. The medication used in this study will be IR MPH/AMPH which is FDA approved for the treatment of pediatric ADHD and the most extensively studied ADHD medication in children.<sup>45</sup> All study drug will be used only for FDA approved purposes (to treat ADHD in children ages 6 to 12) without modification to its approved packaging. It will be administered in its unaltered commercially available form and dosed in accordance with the guidelines outlined in its respective FDA approved packaging. Therefore, according to FDA policy 21 CFR312.2b1, we do not believe that the study requires an IND.

**7.4.2 Treatment Regimen**

The medication assessment procedure was a double-blind, within-subject evaluation of placebo and matching evening dose of IR MPH/AMPH rounded to the nearest 2.5mg increment with a max IR MPH dose of 0.3mg/kg and a max IR AMPH dose of 0.15mg/kg. Expected evening dose range will be from 2.5mg to 20mg with most participants receiving between 5 to 15mg per evening dose. Dose will be determined based on current dose of their morning extended release stimulant. Equivalent dose of ER-MPH is double of ER Dex-MPH.

*Participants will continue on their current dose of morning ER AMPH. For children whose current daily dose is less than 0.15mg/kg/day of IR AMPH, their evening dose will be matched to their daytime dose (e.g. Adderall XR 10mg or Vyvanse 30mg = IR AMPH 5mg). The maximum dose of IR AMPH given will be 10mg.*

AM ER MPH dose for OROS MPH	AM dose of ER non OROS MPH	AM dose ER Dex-MPH	Matching IR MPH dose
18mg	10mg	5mg	5mg
27mg	NA		7.5mg
36mg	20mg	10mg	10mg
54mg	30mg	15mg	15mg
72mg or more	40mg or more	20mg or more	20mg

\*max IR MPH dose of 0.3mg/kg, max dose is 20mg

AM ER Adderall XR	AM dose of Vyvanse	Matching IR AMPH dose
5mg	20mg	2.5mg
10mg	30mg	5mg
15mg	40mg	7.5mg
20mg	50mg	10mg
25mg	60mg	10mg
30mg or more	70mg or more	10mg

\*max IR AMPH dose of 0.15mg/kg or 10mg

Caregivers who have consented to the study will administer the encapsulated drug product to their children (subjects) 3 to 3.5 hours (IR MPH or placebo) before bedtime and **4.5 to 5 hours** (IR AMPH or placebo) *prior to bedtime* over a three week period. Text message reminders will be sent to caregivers if they wish to receive such reminders. Dose will not be increased during the trial but can be lowered if intolerable side effects are reported in increments of 2.5mg. Participants who cannot tolerate an efficacious dose will be discontinued. Blinded medication will be dispensed in containers created by IDS with each daily dose labeled. All participants will only need to take 1 dose a day. Families will be provided with written dosing instructions.

**7.4.3 Method for Assigning Subject to Treatment Groups**

The whole period of active study treatment will last three weeks (21 days). For all participants, it will start on a Friday and end on the third Thursday. Each subject will receive a random mixture of immediate release methylphenidate/amphetamine (IR MPH/AMPH, in a total of 11 days) and placebo (total of 10 days). Each subject will receive IR MPH for 1 day per weekend for each of the three weekends. During the weekday (Sunday to Thursday) subjects will receive at least two

evening dose of IR MPH/AMPH per week for a total of 8 days in the three-week period, resulting a total of 11days (3 days on weekends and 8 days on weekdays) on IR MPH/AMPH over the 21 days of the study. Randomization schedule will be generated by Dr. Junjia (Jay) Zhu, Ph.D., Assistant Professor of Biostatistics at Penn State Hershey Medical Center, and will be directly forwarded to Interventional Drug Pharmacy. Individualized dosing schedules will be provided to the IDS for each participant. Our group has employed similar procedures for within subject trials of CNS stimulants.<sup>37, 40i</sup>

	Week1							Week2							Week3						
	Weekend		Weekday					Weekend		Weekday					Weekend		Weekday				
	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th
ID	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21
1																					
2																					
...																					
37																					
38																					

#### 7.4.4 Subject Compliance Monitoring

Parents will record that time of the ER MPH/AMPH dosing in the morning as well as the IR MPH/AMPH dosing in the evening in the sleep log. Medication adherence will be assessed at each study visit by parent report, review of sleep log and by pill count.

#### 7.4.5 Blinding of the Test Article

IR MPH/AMPH will be blinded using opaque pill capsules with methylcellulose used as the inert placebo ingredient, packaged in matching capsules. All prescribed doses can be fit into one capsule so no participant will need to take more than one capsule a day. All research staff and participants will be blinded to medication assignment. Research staff will be able to access the list outside of pharmacy hours emergently if needed.

#### 7.4.6 Receiving, Storage, Dispensing and Return

##### 7.4.6.1 Receipt of Test Article

The IDS will order, receive, prepare all medication, medication packaging and labels. The IR MPH/AMPH Tablets and placebo will be encapsulated in identical opaque capsules filled with methylcellulose.

##### 7.4.6.2 Storage

With the exception of already dispensed medication, all medication will be stored at the IDS. Study staff will transport medication from the IDS to the research site at 22 NE Drive when needed for participant visits. Study staff will track medication received from the IDS, dispensed to the participant, received back from the participant and then returned to the IDS. All medication onsite at 22 NE Drive will be stored in a locked medication room designed specifically to hold controlled substance medication. It has keypad entry and double locked cabinets. With the exception of already dispensed medication, all medication will be stored at the IDS. In the event of overnight drug storage, a daily count of medication will be documented by a study physician. Documentation will be provided to IDS weekly. Temperature at the NE Drive medication room will be

logged daily. Temperature record logs will be documented daily and documentation will be provided to IDS weekly. Alternatively, participating families may come to the UPC Cancer pharmacy to receive study medication as has been done in other protocols based at HMC. At the dispensing visit, study physicians will verify the participant name on the label matches the name of the child attending the visit. In the study medication database, the ID of the dispensing clinician, the name, dose and amount of the medication as well as the data and subject ID will be recorded. In addition, the amount of prior medication returned by families as well as the amount of medication returned to the IDS will be recorded at each visit.

#### **7.4.6.3 Preparation and Dispensing**

Medication assignment (IR MPH/AMPH dose or placebo) will be randomly assigned per day for the 21 day dosing period. A computer generated randomized medication schedule for the 21 days of treatment will be provided to the Investigational Drug Service (IDS) pharmacy following procedures employed by our research group in past trials of CNS stimulants<sup>37 40</sup>. The IDS will prepare all study medication. IR-AMPH does not come in the dosage required for the study. IR-AMPH has score line and the tablet will be split evenly on the score lines using a pill-splitter, each half will have around IR-AMPH 2.5 mg. IDS pharmacy can visually identify a split between 1.5 mg to 4 mg with confidence. Any split outside of this range of IR-AMPH tablet will be discarded. In the previous trials, dose range of IR-AMPH is between 5-30mg with dose difference range is 5-10mg (Pelham et al, 2001, Regina et al, 2001, Spencer et al, 2006). There is typically no significant difference between doses 5mg apart suggesting that the variance caused by splitting pills will not have a meaningful effect on efficacy or tolerability. For example, in Pelham et al, 2001, meaningful dose differences required a 10mg difference whereas pill splitting should only cause a variance of 1mg or so. Moreover, the slight increase or decrease in milligrams of the dose remains well within the therapeutic window of approved doses of amphetamine (max single dose strength is 30mg).

IR MPH/AMPH will be blinded using opaque pill capsules with methylcellulose used as the inert placebo ingredient, packaged in matching capsules. Study staff will transport medication from the IDS to the research site at 22 NE Drive when needed for participant visits. Study staff will track medication received from the IDS, dispensed to the participant, received back from the participant and then returned to the IDS.

#### **7.4.6.4 Return or Destruction of the Test Article**

Study staff will track medication received from the IDS, dispensed to the participant, received back from the participant and then returned to the IDS. IDS will dispose of returned or unused study medication in accordance with institutional policies as well as state and federal laws.

#### **7.4.6.5 Prior and Concomitant Therapy**

Concomitant medicines that are permitted include Extended Release Methylphenidate/Amphetamine or twice a day Immediate Release Methylphenidate/Amphetamine, as this is required for study eligibility. Alpha agonists prescribed for adjunctive control of ADHD in combination with an MPH product will be allowed as the combination is FDA approved. Current psychotropics other than Methylphenidate/Amphetamine (extended Release or

Immediate Release Methylphenidate/Amphetamine), and regular use of other medications that impact sleep (i.e.: sedating antihistamines, melatonin) are not permitted during the study. Information regarding prior and/or concomitant medical therapy will be collected via phone screen by study staff, and monitored study physicians at each visit. Participants will be allowed to continue with any existing behavioral therapies (e.g. counseling) and will not be restricted from accessing any medical treatments during the course of the study except for those specifically designed to reduce sleep onset latency.

## 8.0 Subject Numbers and Statistical Plan

### 8.1 Number of Subjects

The total number of subjects to be accrued is 38.

### 8.2 Sample size determination

Sample size was determined using Optimal Design software (version 3.01) for a person-randomized repeated measures design with the following assumptions:  $\alpha = .05$ ; power ( $1 - \beta$ ) = .80; observations per condition = 7; standardized treatment effect = .50; between treatment variability = 1.0; within-person (repeated measures) variability = 0.25. The assumption of four times greater variability between-treatments versus within-person is reasonable given past research. Likewise, the treatment effect is supported by prior work that has observed a reduction of SOL by 25% with a late afternoon dose of a IR CNS stimulant, producing an estimated effect size of .5 based on the typical variance in SOL in ADHD youth.<sup>20,30</sup> Taking these assumptions, a power by sample size graph suggests a sample size of 35 participants to achieve statistical power of .78. Based on these calculations and reported attrition rate in previous stimulants studies of approximately 10%,<sup>20,22</sup> an N of 38 subjects is determined to be sufficient.

### 8.3 Statistical methods

The goal of this pilot application is to detect a signal of efficacy that would justify further investment. Treatment effects will be evaluated by conducting linear mixed models in SAS 9.4, with repeated measures nested within persons and with treatment (placebo vs. medication), ADHD symptoms, and ODD symptoms as covariates predicting whether sleep onset latency (SOL) significantly decreases with treatment. We will also evaluate if improvements in SOL will be mediated through reductions in externalizing symptoms in the evening and examine for improvements in other sleep variables including WASO and frequency of nighttime awakenings.

## 9.0 Confidentiality, Privacy and Data Management

See Research Data Plan Review Form for this entire section.

## 10.0 Data and Safety Monitoring Plan

Although the proposed study does not formally meet NIH requirements for the establishment of a Data Safety and Monitoring Board, a plan will be implemented. The principle investigator will oversee the daily safety of participants in the study. If a participating family has an urgent psychiatric concern (expressed suicidal ideation, serious aggression towards others), the principle investigator or the co-investigator (if the principle investigator is unavailable) can be paged 24 hours a day. The families will be provided with a 24-hour emergency contact number. If a serious adverse event occurs, one of the investigators will complete an Adverse Events Form and report the event to the IRB within 24 hours. They will gather information needed to investigate the event and review the adverse event report with the other investigative staff to determine subsequent action.



#### **10.1 Periodic evaluation of data**

Participants will be evaluated by study physicians at first visit (baseline; 1 week), second visit (end of week 1), and third visit (endpoint; week 3). Participants can be brought in for additional study visits as needed to assess tolerability or efficacy concerns. Families will have ability to contact the principle investigator or co-principle investigator 24 hours a day. Families will also be provided with a 24-hour emergency contact number.

#### **10.2 Data that are reviewed**

Data reviewed will include sleep onset latency, other sleep variables, side effects of study medication using the Pittsburgh Side Effect Rating Scale as well as spontaneous report, vital signs, concomitant medications, levels of ADHD /ODD symptoms and degree of parent rated irritability.

#### **10.3 Method of collection of safety information**

Methods of collection of safety information include study visits (parent ratings, direct observation actigraphy) and direct feedback from children.

#### **10.4 Frequency of data collection**

Safety data collection starts at the baseline visit (visit 2) . The same parameters will be collected at end of week 1 (visit 3) and final safety data collection also occurs at the end point visit (week 3). Families also have the ability to contact the principle investigator or co-principle investigator 24 hours a day for three weeks, resulting in the possibility of ad hoc data collection. Additional study visits can be scheduled as needed.

#### **10.5 Individuals reviewing the data**

Study physicians and study investigators will be reviewing the data. If a serious adverse event occurs, one of the investigators will complete an Adverse Events Form and report the event to the IRB within 24 hours. They will gather information needed to investigate the event and review the adverse event report with the other investigative staff to determine subsequent action.

#### **10.6 Frequency of review of cumulative data**

All side effect data will be reviewed at the time of collection by MD study staff.

#### **10.7 Statistical tests**

N/A Rates of side effects as captured on the PSERS within subjects between the medication and placebo will be analyzed by repeated measures ANOVA.

#### **10.8 Suspension of research**

Any participant experiencing a 50% worsening in sleep onset latency that cannot be corrected by lowering the prescribed dose will be discontinued from the study. Further, study investigators will determine if a discontinuation from the study is appropriate due to any other adverse reaction to the Immediate Release Methylphenidate/Amphetamine. While it is unlikely, as these participants will have had exposure to Methylphenidate treatment, the suspension of research may be required if severe adverse reactions including hypertension or other cardiac problems, other cardiovascular conditions, worsening behavioral problems including aggression and , psychotic symptoms, seizures, or acute visual disturbances. Participants may be withdrawn from the study at any point in time if safety concerns arise. , or safety concerns.

### **11.0 Risks**

1. Risk: The primary risk to participants includes any potential adverse reactions to the Immediate Release Methylphenidate (IR MPH) or Immediate Release Amphetamine (IR AMPH) treatment. The side effect profiles of IR MPH and IR AMPH are largely similar with the two medications primarily differing in their potency and duration (Pelham et al, 1999, Greenhill et al, 2002). Common side effects include decreased

appetite and weight loss, irritability, sleep difficulties (however, it is theorized that many participants will experience decreased sleep latency secondary to better control of ADHD symptoms), increases in blood pressure and pulse, headaches, jitteriness, motor/verbal tics. Rare side effects include visual disturbances, serious cardiovascular problems, aggression, mania or psychotic symptoms, seizures, or visual disturbances. These rare side effects are generally confined to those with preexisting health problems in those realms (e.g. a personal history of structural heart defects, psychoses or mania). The risk of concerning side effects should be low as all participants will have had to be on a stable morning dose of a methylphenidate/amphetamine product for at least the past 30 days. Hence, no participant will be newly treated with methylphenidate/amphetamine. Families will have 24 hour access to investigative staff should any adverse reactions occur, and medication status can be unblinded on an emergent basis if needed.

2. Risk: Participants (children or family) may become distressed as a result of having to cease current Methylphenidate treatment for two days during the intake assessment process to determine study eligibility. Parents are allowed to pick what days this will be to minimize risk. Many parents routinely opt not to give medication on weekends and drug holidays are clinically prescribed to improve weight gain. Therefore, it is not uncommon for children to intermittently skip medication doses. There is no risk of withdrawal side effects with CNS Stimulants.

3. Risk: Participants (including child participant and families) may become distressed due to the increases in ADHD symptoms on placebo versus methylphenidate/amphetamine. All participants are randomized to receive treatment with placebo for 10 out of 21 of the study days. However, all will be continued on their morning dose of methylphenidate so there should be no difference in daytime symptom control. The increase in night time ADHD symptoms with placebo should be no different than pre study levels.

4. Participants (children or family) maybe stressed due to time commitment and completing the necessary ratings and visits. We have selected relatively brief measurements to minimize this risk and participants can refuse to complete any measure they chose.

5. Risk: Primary caregivers may become distressed by the sensitive nature of some of the questions being asked. Most questions are similar to those encountered in routine clinical care for ADHD or sleep problems. They can refuse to answer any questions they are not comfortable with.

6. Risk: Loss of confidentiality.

## 12.0 Potential Benefits to Subjects and Others

### 12.1 Potential Benefits to Subjects

We anticipate a potential direct benefit to the parents and their child as a result of their participation in this research study. Participants will receive an assessment by a mental health specialist that evaluates whether their child meets criteria for Attention Deficit Hyperactivity Disorder (ADHD) or one of its subtypes, as well as sleep disorder and/or other psychiatric conditions that commonly co-occur with these conditions (i.e.: depression, anxiety, oppositional defiance disorder, conduct disorder). They will also be treated with Immediate Release Methylphenidate/Amphetamine (a FDA approved ADHD treatment) by clinicians who are experts in the management of ADHD, BIC and oppositional behaviors. All of these services will be provided free of cost. Children can benefit from this study by displaying improvements in their sleep and behavior problems in the evening hours. Oppositional behaviors have been identified as a major cause of sleep problems in ADHD youth. The information gained from the study may also help parents, clinicians, and educators working with the children with sleep and behavioral problems to develop more effective intervention programs.

## **12.2 Potential Benefits to Others**

Clinical science may gain further understanding in the alternate treatment methods of Behavioral Insomnia of Childhood in school-aged youth with ADHD.

## **13.0 Sharing Results with Subjects**

Upon completion of the study, participants will be provided with their own treatment summary report, which includes the results of the initial diagnostic assessment, as well as specific feedback about the participant's progress during the intervention. We will also share sleep logs and actigraphy data with the participants.

## **14.0 Subject Stipend (Compensation) and/or Travel Reimbursements**

All services will be provided at no charge. Parking is free at the HMC campus and the 22 Northeast Drive Clinic. Families will not be reimbursed for travel costs. Families will receive a \$50 gift card to a local store that offers child appropriate items (Walmart, Toys 'r' Us, Target), for completion of the endpoint measures. The gift card being provided is to promote timely completion of assessment and to offset the cost of travel. The maximum compensation will be \$50 per family. Parents will only be compensated for completed assessment visits.

## **15.0 Economic Burden to Subjects**

### **15.1 Costs**

Participating families will not be reimbursed for other expenses relating to the study such as transportation. All treatment provided, study visits, telephone contacts, and physical and psychiatric evaluations will be provided free of charge. Standard or emergency medical care provided outside of this study (taking the child to see their pediatrician) will not be covered or reimbursed for the participant or the participant's parent(s)/guardian. For text reminders, regular text message rates and charges will apply as per the family's mobile phone plan. Families will not be reimbursed for any incurred costs related to the reminder text messages.

### **15.2 Compensation for research-related injury**

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to participants or their insurance carriers.

## **16.0 Resources Available**

### **16.1 Facilities and locations**

Participants will be recruited from pediatric and psychiatry outpatient clinics within the Hershey medical Center. The Attention and Behavior Clinic (ADHD research site) is also housed at 22 NE Drive. Assessments will be completed at 22 Northeast Drive, which has ample space for research. Dr. Baweja, Dr. Waxmonsky, Dr. Waschbusch and Dr. Calhoun are on faculty at Penn State College of medicine in the Department of Psychiatry.

### **16.2 Feasibility of recruiting the required number of subjects**

Over 3,000 children with Disruptive Behavioral Disorders are seen at Hershey Medical Center each year. Given the prevalence of Behavioral Insomnia of Childhood in such youth, recruiting a total of 38 participants should not be problematic.

### **16.3 PI Time devoted to conducting the research**

One calendar month

#### 16.4 Availability of medical or psychological resources

Treatment will be provided at the 22 Northeast Drive, Penn State Hershey Medical Group Psychiatry Clinic. Parents interested in additional psychological or psychiatric services for their child(ren) may be directed to these additional services or can be directed to other providers in the area for their child's mental health needs. Any child that needs a more formal sleep assessment or other medical interventions for a sleep disorder will be referred to the HMC Pulmonary Sleep Center where Dr. Calhoun provides clinical services.

#### 16.5 Process for informing Study Team

The study team can be updated during regularly scheduled meetings or any time through e-mail or phone.

### 17.0 Other Approvals

#### 17.1 Other Approvals from External Entities

N/A

#### 17.2 Internal PSU Committee Approvals

**Check all that apply:**

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of the Use of Human Tissue For Research Form on the “Supporting Documents” page in CATS IRB. This form is available on the IRB website at:

<http://www.pennstatehershey.org/web/irb/home/resources/forms>

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload the Radiation Review Form on the “Supporting Documents” page in CATS IRB. This form is available on the IRB website at: <http://www.pennstatehershey.org/web/irb/home/resources/forms>

☐ IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: <http://www.pennstatehershey.org/web/irb/home/resources/investigator>

## 18.0 Multi-Site Research

N/A

## 19.0 Adverse Event Reporting

### 19.1 Adverse Event Definitions

### 19.2 Recording of Adverse Events

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy

NOTE: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.

- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study

The test finding is considered an adverse event by the investigator.

Common side effects of IR MPH include appetite loss, headache, moodiness or irritability, problems falling asleep, feelings of nervousness, nausea, dizziness, stomachaches, skin rashes, drowsiness, motor movements (particularly of the mouth, jaw and tongue), and social withdrawal. Most side effects are mild and improve after says days on the medication, including problems falling asleep. The medication may also cause an increase in heart rate or blood pressure and can affect seizures in children with seizure disorders. Therefore, some children with heart problems or seizure disorder should not use this medication and will be determined as ineligible for the study. A study physician will ask subjects if they have experienced any of these problems. All subjects will have access to a 24/7 telephone number to report any of these symptoms or other adverse reactions as well.

### 19.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

#### **19.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA**

All study drug will be used only for FDA approved purposes (to treat ADHD in children ages 6 to 12) without modification to its approved packaging. It will be administered in its unaltered commercially available form and dosed in accordance with the guidelines outlined in its respective FDA approved packaging. Therefore, according to FDA policy 21 CFR312.2b1, we do not believe that the study requires an IND. An RQA consult also determined that an IND was not necessary.

##### **19.4.1 Written IND/IDE Safety Reports**

N/A

##### **19.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions**

N/A

#### **19.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB**

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

#### **19.6 Unblinding Procedures**

If the need arises, research staff will contact the research pharmacy to identify the medication that was given on a specific date. Research staff will be able to access the list outside of pharmacy hours if emergently needed.

#### **19.7 Stopping Rules**

N/A

### **20.0 Study Monitoring, Auditing and Inspecting**

#### **20.1 Study Monitoring Plan**

##### **20.1.1 Quality Assurance and Quality Control**

N/A

##### **20.1.2 Safety Monitoring**

N/A

### **21.0 Future Undetermined Research: Data and Specimen Banking**

N/A

### **22.0 References**

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