PennState

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

Protocol Title:

Neurophysiological Markers of Pediatric Irritability and its Response to Intervention

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Table of Contents

1.0 Objectives

1.1 Study Objectives

There has been an increasing focus on the adverse impacts of irritability, defined as increased tendency towards anger.[1] In children, irritability manifests as a persistently negative mood and frequent temper outbursts.[2] Severe, persistent irritability has been conceptualized as Disruptive Mood Dysregulation Disorder (DMDD) with 3% of children meeting criteria for it.[3] Most youth with DMDD have Attention Deficit Hyperactivity Disorder (ADHD)[4] but only a subset of patients with ADHD exhibit impairing irritability.[5] Even in children not meeting full DMDD criteria, irritability causes a range of impairments[6,7] and is a risk factor for depression, suicide and substance use.[8] Irritability has been identified as transdiagnostic entity meriting investigation as a target for personalized intervention.[9] Irritability levels are only minimally correlated with severity of ADHD symptoms or impairments in executive functioning, suggesting that irritability is distinct and not simply a manifestation of severe ADHD. [5,10] Presently, the first line treatment for irritability in children with ADHD is to optimize the dose of the CNS stimulant. [11,12] However, there is great heterogeneity in response, with some children experiencing complete remission of their irritability and others experience worsening irritability.[11,13] Increased irritability is one of the most common reasons why parents stop these medications.[13] It is unknown what drives this heterogeneity in response as no reliable treatment markers have been identified. The unpredictability of CNS stimulants has led to the increasing use of atypical antipsychotics for the off label treatment of ADHD.[14,15] While effective, these medications are associated with concerning side effects.[16]

In order to identify markers of treatment response, it is necessary to delineate the causal pathways underlying irritability. However, the mechanisms driving irritability are largely unknown. Two areas theorized to contribute to irritability are impairments in learning from experience (instrumental learning) and sensitivity to reward and loss.[1] There are objective, reliable methods for measuring these domains in children through the use of event related potentials (ERPs), synchronous neural activity derived from the electroencephalogram (EEG) in response to a stimulus. Reward positivity (RewP) is an ERP occurring in response to feedback on task performance that can be broken down to separately analyze response to gain (delta frequency) and loss (theta frequency).[17] No prior work has examined these components of RewP with irritability but others have found unique associations of each with depression. As irritability is an established risk factor for depression,[6,18] it is reasonable to surmise that RewP may predict irritability as well. Error related negativity (ERN) reflects the preconscious detection of potential conflict, serving as an early warning signal for errors and a first step to adapting behavior in response to achieve a desired goal (e.g., instrumental learning.)[19] A subset of children with ADHD exhibit a suppressed ERN on cognitive tasks, and ERN amplitude is associated with task performance.[20,21] When suppressed, CNS stimulants normalize ERN, which is correlated with improved task performance.[22]

We theorize that abnormalities in RewP to reward and loss on a monetary guessing task will predict the severity of irritability, while ERN amplitude on a response inhibition task will predict the degree of improvement in irritability after dose optimization of CNS stimulants. These associations will be assessed in 47 children with ADHD and elevated levels of irritability using daily parent ratings gathered before and after optimization of CNS stimulant. To address the great variability in a child's daily behavior, we will use the recommended collection format of ecological momentary assessment (EMA) to gather multiple daily ratings of irritability.[1] Lastly, there is a longstanding concern that CNS stimulants may lead to rebound irritability late in the day as their effects fade.[13,23] It is unclear if this simply represents a return to the premedication baseline that parents perceive as more severe after observing improved behavior earlier in the day or a true worsening in irritability. Therefore, we will use EMA to compare changes in irritability during medicated times of day versus unmedicated times, theorizing that greater daytime improvement will be associated with parents rating worse evening behavior.

Aim1: Examine the capacity of lab measurements of reward sensitivity to predict irritability in ADHD children

H1: After controlling for relevant covariates, gain-related delta and loss-related theta activity in the EEG during a reward-guessing task will each correlate with levels of the child's irritability reported at home.

H2: Children with elevated levels of both loss related theta & gain-related delta will exhibit the greatest irritability.

Aim2: Examine the capacity of ERN amplitude during a response inhibition task done in the unmedicated state to predict the capacity of CNS stimulants to reduce irritability in children with ADHD.
H1: Smaller baseline ERN will predict greater improvement in irritability with optimization of stimulant dose.
Aim3: Examine the phenomena of rebound irritability with wear-off of the therapeutic effect of CNS stimulants.
H1: Greater reductions in irritability when the CNS stimulant is active (vs when it is inactive) will be associated with parents reporting increasing irritability after the stimulant has worn off.

1.2 Primary Study Endpoints

The primary outcome in this study will be the change in parent rated irritability on the DBD irritability score. Symptom severity for ADHD symptoms, irritability and other symptoms Oppositional Defiant Disorder (ODD) will be assessed using the Disruptive Behavior Disorders (DBD) Parent Rating Scale rating symptoms on a 0-3 likert[24] and the Clinical Global Impressions Severity Score (CGI-S) ADHD scale (Guy 1976) will serve as the ADHD efficacy measures.

1.3 Secondary Study Endpoints

Parents will enter two ratings a day through a survey application that can be downloaded to their own smartphone or tablet at preselected times when the medication is active (afternoon) and when it has worn off (evening) with exact rating times individualized per family. We have used similar EMA protocols in other studies and expect that >85% of the ratings will be completed.[25] At baseline (prior to dose optimization) and endpoint (after dose optimization), parents will complete the Impairment Rating Scale (IRS) to measure functioning across multiple domains,[26] the Modified Overt Aggression Scale (MOAS)[27] and Inventory of Callous Unemotional Traits[28] to measure aggression, the Affective Reactivity Index[29] as an additional measure of irritability, and the Pittsburgh Side Effects Rating Scale (PSERS) to evaluate side effects.[30]
We will also examine if loss and gain sensitivity on the ERP will be positively correlated with parent ratings of irritability. For Aim 2, we will examine if ERN amplitude in the response inhibition task when unmedicated will be inversely correlated with degree of improvement in irritability following optimization of CNS stimulant dose.

2.0 Background

2.1 Scientific Background and Gaps

There has been an increasing focus on the adverse effects of irritability, defined as increased tendency towards anger.[1] Irritability and aggression are the main reason why children enter mental health treatment.[31] Irritability worsens peer relationships, family functioning, and academic performance.[2,6,18] It is a risk factor for depression, suicide, substance use and unemployment.[8,18] Severe persistent irritability coupled with excessive temper outbursts has been conceptualized as DMDD in the DSM-5.[32] Most children with DMDD will meet criteria for ADHD,[4] and 30-50% of children with ADHD manifest impairing levels of irritability.[5] Yet there is only a mild correlation between irritability and severity of ADHD symptoms,[5,10] suggesting that irritability is not just a sequala of severe ADHD. In fact, irritability has been identified as transdiagnostic bridge between internalizing (distress directed inward) and externalizing psychopathology (distress directed outward),[9] meriting investigation as a treatment target for personalized intervention, given its prevalence and morbidity.[1,33]
Significant advances have been made in understanding the neural circuits for the related constructs of aggression and emotion regulation,[9] but less is known for irritability. The National Institute of Mental Health (NIMH) recently proposed that irritability stems from 1) impairments in instrumental learning (adjusting behavior in response to feedback), for which the capacity to detect if a behavior is leading to a desired effect (error predication) is a necessary step 2) inhibition and 3) sensitivity to reward/loss.[1] As impaired response inhibition is a core deficit in ADHD,[20] only impairments in the other two realms are needed to produce irritability in ADHD youth. There are established means in children to measure

neurophysiological and behavioral abnormalities in reward/loss sensitivity and error prediction but they have never been jointly applied to assess irritability.

Existing treatments for irritability focus on comorbidity. In ADHD, irritability can be improved by optimizing the Central Nervous System (CNS) stimulant dose.[11,12] However, irritability is a common side effect of CNS stimulants, often leading to discontinuation.[5] Even when effective, many parents report worse irritability than before treatment as the medication wears off, called rebound irritability.[5,13,23] It is unknown what drives this heterogeneity and unpredictability in response to CNS stimulants has contributed to increasing use of antipsychotics and other nonevidence-based treatments for ADHD.[14,34] These treatments can be associated with obesity, cognitive impairments and a host of other adverse effects.[16] Identifying a reliable marker for the tolerability and efficacy of CNS stimulants in youth with ADHD and prominent irritability would greatly reduce the need for these off-label treatments while advancing the creation of personalized treatment algorithms for children with this common but impairing presentation. Elucidating the mechanistic pathways for irritability would also aide the development of additional psychosocial and medication treatments as CNS stimulants rarely normalize irritability in youth with ADHD.[12,35]

2.2 Previous Data

N/A

2.3 Study Rationale

Over 10% of American youth are diagnosed with ADHD.[36] Up to half of these youth exhibit impairing levels of irritability that predict a wide array of negative outcomes.[2,5] Current treatments for irritability focus on maximizing control of ADHD symptoms with CNS stimulants but that can lead to worse or improved irritability.[13] There are no reliable markers of response due in part to a limited understanding of what drives irritability. Delineating the mechanism underlying mental health symptoms enables creation of treatments directly targeting measurable irregularities in neural circuitry.[37] We propose that reward and loss sensitivity are markers for irritability in children with ADHD.

Electroencephalography (EEG) has been widely used to assess neural activation patterns underlying instrumental learning and reward sensitivity.[17,38] It offers reliable assessment of neural activity in children and is more economical and less burdensome than MRI, making it an ideal method for translating neuroscience into clinical practice. When the EEG recording is locked to a specific stimulus, the associated synchronous neural activity is an event-related potential (ERP). EEG allows a precise assessment of the timing of neural activity so that a complex behavior (e.g. Instrumental learning) can be broken down into a series of simpler events.[17]

Abnormal sensitivity to reward and loss is theorized to drive increased goal seeking behavior and frustration when blocked from a goal that are common in irritable youth.[2] Initial studies have found links between irritability and increased reward sensitivity.[1] For example, Kessel et al. found evidence of enhanced reward positivity (RewP) in children with a history of irritability as preschoolers.[39] RewP is an ERP that occurs 300ms after observable feedback about receipt or loss of a potential reward[40] and is an established neural marker of reward sensitivity in children.[17,39] Interestingly, ADHD has also been associated with an elevated RewP.[41] The high comorbidity between irritability and ADHD[4] could explain these associations and suggests it is important to account for ADHD when examining links between RewP and irritability. On the other hand, a blunted RewP has been identified as a risk factor for depression.[17,42,43] As irritability is also a well-established risk factor for depression,[2] it is surprising that associations with RewP and irritability are in opposing directions than for those for RewP and depression. Distinct responses to gain and loss may be one explanation for these findings. That is, when examined using time frequency approaches, responses to loss are reliably associated with higher frequency theta activity, while gain is associated with lower frequency delta activity,[40] which contribute to the amplitude of RewP in combination. While moderately correlated with each other, theta and delta activity are distinct such that one can be elevated and the other suppressed.[44] Loss components have been localized to the anterior cingulate cortex (ACC) in response to a drop in dopamine (DA) triggered by a worse than expected event, and gain components originate from the ventral striatum when there is a DA rise due to a better than expected event.[44] Relatively few studies of RewP in psychiatric disorders have evaluated these two

frequency bands, and failure to consider the unique associations with gain and loss responses may have contributed to these opposing RewP findings. For example, in one of the few studies to dissect RewP in depression, both hyposensitivity to reward and hypersensitivity to loss were associated with depression.[45] No prior work has used time frequency analyses to examine these components of RewP in children with prominent irritability. We theorize that irritability may stem from elevations in both sensitivity to reward causing more reward seeking behavior and sensitivity to loss causing increased frustration when goals are not met. These dual elevations could manifest as a suppressed or elevated RewP depending on their relative amplitudes. RewP is thought to reflect a relatively stable trait,[17] and there is no evidence that itis impacted by CNS stimulants.[38] Therefore, we hypothesize that it will not correlate with the amount of improvement in irritability seen with optimization of CNS stimulants, although this has never been explored.

Early preconscious detection of a potential error (conflict between what was expected and what is produced) leads to an ERP component called error-related negativity (ERN).[38] ERN is an early neural warning sign that a change in behavior may be needed and can be reliably measured in children as young as 5 using a variety of cognitive tasks.[19,46] ERN amplitude is correlated with error checking capacities, executive functioning and even academic performance. Increased ERN amplitude is associated with improved performance on a range of neurocognitive tasks, to the degree that is has been proposed as a transdiagnostic marker for instrumental learning capacity.[19,41] In contrast, suppressed ERN is associated with impulsivity and other behavioral problems.[47] Interestingly, impaired instrumental learning is more associated with irritability and other oppositional behaviors than with ADHD.[48] The combination of a suppressed ERN and childhood irritability predicts worsening behaviors problems than either one alone,[47] suggesting that enhancements in error detection may also reduce future behavioral problems.

ERN has been localized to the ACC, with activation occurring in response to a drop in DA tone when potential conflict is preconsciously detected in the basal ganglia.[49] Interestingly, youth with DMDD have been found to exhibit hypoactivation in the ACC and striatum[50,51] when task performance is rigged to provide worse than expected outcomes. Likewise, ADHD is associated with reduced DA tone in the striatum at rest and in anticipation of reward.[38,52] DA agonists including CNS stimulants increase DA tone in the ACC and striatum[52] and can normalize a suppressed ERN in children with ADHD and healthy controls.[22,49] These changes correlate with improvements in error detection and response accuracy.[20] It has been theorized that an abnormal ERN may be modifiable and therefore serve as a marker of treatment responsivity in multiple disorders.[19,20] However, ERN's association with irritability and treatments for it have not been examined.

In summary, impairments in reward sensitivity and instrumental learning are theorized to drive irritability, especially in youth with ADHD. RewP has been established as marker of reward sensitivity that can be parsed to separately examine neurophysiological reactions to loss and gain. ERN measures one of the earliest steps in instrumental learning, with a suppressed ERN associated with impaired cognitive performance. RewP is thought to be stable, but ERN may be malleable with CNS stimulants enhancing it. Therefore, we theorize that in children with ADHD and prominent irritability, loss and gain sensitivity will be positively correlated with parent ratings of irritability and ERN amplitude when unmedicated will be inversely correlated with degree of improvement in irritability following optimization of CNS stimulant dose.

This will be the first study to assess these associations in an ADHD sample and the first to use time frequency analysis to examine the unique associations of sensitivity to loss and reward with irritability. There is evidence that ERPs may be useful predictors of CNS stimulants' capacity to improve instrumental learning and other aspects of cognitiion.[20,53] There are no current markers of response for any medication for pediatric irritability. We propose that a suppressed ERN will serve as a marker for the capacity of CNS stimulants to improve irritability. These associations will be assessed using ecological momentary assessment (EMA), the collection of repeated measures in the natural environment linked to a specific time or event. It is the recommended format for measuring irritability.[1] If successful, we will have verified a theorized circuit of impairment, identified an objective measure (RewP) that can identify at-risk youth and a potential treatment marker (ERN) for irritability in children with ADHD. Results will be used to develop translationally informed care algorithms for irritability that could reduce rates of antipsychotic prescription, [14] and thereby improve outcomes while reducing treatment related morbidity. We will also

use EMA to examine the frequency of rebound irritability with CNS stimulants, a widely reported but little studied phenomena and a major reason why clinicians are hesitant to use CNS stimulants in irritable youth.[13] It is theorized that rebound irritability primarily stems from parents interpreting wear-off of therapeutic effects of CNS stimulants over the course of the day as increased irritability.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. Age at time of enrollment: 5-12 (inclusive)
   CNS stimulant medications are commonly used in studies within this age range, and this is the age range where children are most likely to present for treatment of irritability. [1]
2. Meets diagnostic criteria for any presentation type of ADHD. ADHD status will be assessed on the NIMH Computerized Diagnostic Interview Schedule for Children (C-DISC).[54] The C-DISC will also be used to assess psychiatric comorbidity, with diagnoses confirmed by an MD/PhD prior to eligibility decisions. Symptom severity for ADHD, irritability and Oppositional Defiant Disorder (ODD) will be assessed using the Disruptive Behavior Disorders (DBD) Parent Rating Scale which is similar to the Vanderbilt, rating symptoms on a 0-3 likert.[24] In accordance with previous studies of irritability in ADHD, the DBD irritability score (range 0-9) will be the primary outcome, with a moderate level of irritability (≥5) required for entry.[12] DMDD status will be assessed using Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (KSADS-PL)[55] given to parent and child but DMDD will not be required for entry as subthreshold levels of irritability produce significant impairment.[7]
3. Male or female
4. Fluent in written and spoken English.
5. Parent must have a smart phone or tablet device to complete EMA ratings.

3.2 Exclusion Criteria

1. Age <5 years of age or >12 years of age.
2. Children with significant visual or hearing deficits or sensitivity to loud noises as test performance requires intact hearing and vision.
3. Serious neurological conditions that impacts cognition, such as an active seizure disorder
4. Current psychotropics other than FDA approved ADHD medications, as medication will be withheld on testing days. Unlike most other psychotropic medications, CNS stimulants can be withheld for brief periods and acutely restarted with no safety risks and lengthy titration process. Numerous ADHD studies have safely withdrawn these medications or substituted inert placebo for testing or clinical observation.[56,57] Children taking an approved nonstimulant for ADHD plus a CNS Stimulant medication will be allowed to participate and will just have their CNS stimulant dose withheld on testing days.
5. Prominent traits of autism spectrum disorder (Social Communication Questionnaire Score >15), marked developmental delay or psychiatric conditions requiring urgent treatment (mania, psychoses, suicidal ideation).
6. Parent or child not fluent in English
7. Parent that does not have a smart phone or tablet device to complete EMA ratings.

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.

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.

4.0 Recruitment Methods

4.1 Identification of subjects

Participants will be identified in several ways:

- By the PI/SI during a patient clinic visit and/or from patient referrals
- Database search – A member of the research team will query the Psychiatry database to identify subjects meeting the inclusion/exclusion criteria who previously gave permission to contact regarding new studies.
- A member of the research team will review clinic scheduling calendars and medical records to identify potential research subjects. Review of medical records may be used to determine preliminary eligibility for the research study.
- Use of recruitment materials: flyers, STUDYfinder, Penn State Children's Hospital research page, Facebook advertisements (study flyers) and links, CareLine, on-hold messages

4.2 Recruitment process

Potential subjects calling in response to recruitment materials will be screened using the attached telephone eligibility-screening document.

A member of the research team will explain the study to the subject at the time of the prospective subject's clinic visit.

4.3 Recruitment materials

STUDYfinder
Recruitment documents attached in CATS:

- 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 screen 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

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

A waiver of consent is requested to review medical record information to determine preliminary eligibility to participate in the research.

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

The consent process will be documented in writing with the long form of consent documentation:

- The current IRB approved consent form will be obtained.
- We will verify that we are using the most current IRB-approved version of the study specific consent form and that the consent form is in language understandable to the subject/representative.
- A copy of the consent form will be provided to the subject/representative. Whenever possible the consent form will be provided to the subject/representative in advance of the consent discussion.
- If the subject/representative cannot read we will obtain an impartial witness to be present during the entire consent discussion to attest that the information in the consent form and any other information provided was accurately explained to, and apparently understood by, the subject/representative, and that consent was freely given.

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 to determine study eligibility.

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects

N/A

5.3.2 Cognitively Impaired Adults

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 5 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 for assent 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

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Study information will be retained all institutional/regulatory requirements for data retention have been met.

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

Information must be obtained from the subject's electronic medical record during recruitment to determine eligibility and, in some cases, to confirm information discussed with the subject in regards to their medical history.

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

The waiver is requested only for recruitment to determine subject eligibility to ensure that no medical conditions that fall into the exclusion criteria are present and would thus preclude enrollment. This waiver will minimize the enrollment of subjects' who may ultimately fail to meet the study inclusion/exclusion criteria.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

We will recruit 47 children with ADHD and elevated irritability to examine neurophysiological markers of irritability and its responsiveness to CNS stimulants. Visit 1 will consist of consent/assent and assessing eligibility. Collection of neurophysiological markers while the child is unmedicated will occur at visit 2. This will be followed by 1 week of baseline assessments of ADHD symptoms and irritability manifesting at home collected using EMA, followed by a up to 12-week open label titration of the child's CNS stimulant. Endpoint will consist of 1-week assessment of irritability and ADHD symptoms using the same EMA battery collected on the optimal CNS stimulant dose. At each point, we will collect separate ratings for medicated and unmedicated times (early morning before med is active or evening when med has worn off) of day to assess the impact of medication wear-off on irritability.

Visit 1 (2 hours)	Visit 2	Baseline EMA assessment (1 – week duration)	Visit 3-8 Open label medication trial	Endpoint EMA assessment (1 – week duration)	Visit 9 (final visit)
Consent/assent baseline assessments	Collection of neuro-physiological markers	Parents will compete daily ratings of their child's irritability and ADHD symptoms at home	12-week open label titration of their CNS Stimulant to optimize control of their ADHD symptoms at home. participants will be evaluated by	Parents will complete daily ratings of their child's irritability and ADHD symptoms using the same EMA procedures on their optimal dose of CNS stimulants.	Parents will complete the final ratings for side effects of CNS stimulants, and collect study material.

			study physicians on weekly basis.		

7.2 Study Procedures

7.2.1 Visit 1 (Intake)

Participation will involve an approximately two-hour intake appointment where theparticipating 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. Participant vitals (height, weight, blood pressure, and pulse) will be obtained and they will be interviewed using the KSADS DMDD (identical to the parent version) module to assess their perception of how they control their temper (average duration 15 minutes). In the clinical setting, the parent and teacher complete the questionnaires. Therefore, we are also asking the parent's permission to send to the child's teacher the identical validated teacher questionnaires (IRS and DBD-RS) to assess the level of ADHD symptoms and impairment in school. The teacher will be informed that the family is participating in a research study for which it is necessary to collect an assessment of the child's level of ADHD symptoms in the classroom. No PHI of the child will be linked to the questionnaires the parent or teachers completes, including the one used to make ADHD diagnosis.

7.2.2 Visit 2 (Testing)

After obtaining consent, all intake tests will be completed in a single testing day when the child has not taken their CNS stimulant. These medications are routinely stopped in clinical trials for ADHD without adverse effects other than an increase in ADHD symptoms for the day.[56]

Reward and loss sensitivity will be measured by the Doors task.[42] On each of 60 trials, participants see two doors on a computer screen and guess which door has a prize behind it followed by a feedback arrow (green upward arrow indicates a win of $0.50/red downward arrow indicates a loss of $0.25) with children told they get to keep earned money up to $10. In reality, there are equal numbers of reward and loss feedback in each condition and all participants earn a $10 gift card at the end of the task. EEG data will be recorded using a 32-channel BrainProducts actiCHamp system and BrainVision Recorder software with electrodes placed over the left and right mastoids as reference electrodes and above and below the eyes to measure eye movements. Data will be processed offline using BrainVision Analyzer software. EEG data will be segmented beginning 500ms prior to and continuing for 1000ms after feedback. Each trial will be filtered and corrected for eye movements and artifacts, averaged separately for gains and losses, and baseline corrected. Consistent with prior work,[45] a complex Morlet wavelet transformation will be applied to processed EEG data using Brain Vision Analyzer software, with the results of the wavelet transformation averaged for each condition (gains, losses) for a measure of total power. Wavelet layers corresponding to delta power and theta power will be extracted approximately 250-400ms after feedback at centroparietal sites for delta and frontocentral sites for theta.

To measure error detection, participants will complete a well-established Go/No-Go task, which reliably elicits an error-related negativity (ERN) in children. Participants will be shown a green triangle in one of four orientations presented on a black background: most triangles will be vertically aligned and pointed upward, with a subset vertically aligned and pointed downward or tilted slightly to the left or right. Participants will be instructed to press a button only when the vertically aligned upward-pointing triangle is presented (Go stimulus) and to inhibit responses for the others (No-go stimuli). Participants will first complete practice trials with feedback, and will then complete up to 240 trials (7-10 minutes).

As there is some evidence that abnormalities in the ERN may be more apparent when within-subjects variation in error rates is restricted[89], we will also pilot a newer task that dynamically adjusts stimulus presentation time based on participant performance. This task will be administered following completion of the reward and triangles task (presented in a counter balanced order) when time permits and participants are motivated to complete an additional task. To minimize participant fatigue and because data collected from this task will only be used for pilot data, we will skip this task for any children who are having difficulty concentrating or remaining motivated to complete tasks. In this task, participants will see an asteroid (Go stimulus) or space ship (No-Go stimulus) on the screen, instead of triangles, and be instructed to press a button when the asteroid appears and inhibit responses to the space ship. Stimulus presentation time will shorten with repeated correct answers and lengthen with repeated errors to minimize between subject variance in number of errors. Participants will complete practice trials with feedback and up to 240 trials (5-7 mins).

Participants will be informed that they can earn a prize for trying their best on these tasks, and all participants who complete one or both error tasks will be given a prize.

Children will not be rewarded for completing this task as incentives can normalize ERN amplitude.[38] EEG data collection and processing will be similar to procedures used for the Doors task (see above). The ERN will be evaluated as the average voltage in the window 0 to 100ms after error responses over frontocentral electrode sites.[46] Error-related positivity (Pe), which is thought to measure of conscious awareness of error, will also be assessed, as it has been found to be impaired in ADHD and may improve with CNS stimulants.[38,58]

7.2.3 Baseline EMA Assessment (1 week duration)

Parents will complete daily ratings of their child's irritability and ADHD symptoms at home over a 7-day baseline period using EMA prior to any adjustment of the child's ADHD medication. The primary measure will be the IOWA Conners[59] supplemented to include all 3 irritability items from the DBD. This 12-item rating takes only minutes to complete. Parents will enter two ratings a day through a survey application that study staff will download and install on the parent's smartphone or tablet (whichever is preferred).Notifications for these surveys will be automatically administered at preselected times when the medication is active (afternoon) and when it has worn off (evening) with exact rating times individualized per family.

LifeData, LLC is the company that provides the interface for the survey batteries. LifeData, LLC services is HIPAA compliant and have been used by leading institutions including Massachusetts General Hospital, Harvard University, Yale University, UNC School of Medicine, USC University of Southern California, UC Davis, and Indiana University. [135] LifeData, LLC services have been approved by other university IRBs for clinical research including Children's Hospital of Philadelphia,[133] Indiana Wesleyan University, [134] and University of Sydney, [136] to name a few. LifeData, LLC keeps participant data private and does not share or sell the information. LifeData, LLC holds no ownership of the data. LifeData, LLC does not have access to participant information outside of the LifeData app. LifeData, LLC has access to GPS coordinates based on when surveys are completed; however, participants are given the option to allow or disallow this option at the beginning of the app set-up. If participants allow for LifeData to collect GPS coordinates, they may later disallow the option by going through their device's settings and LifeData app options. LifeData, LLC also collects the unique mobile device identification number, which informs LifeData and this research study team if the participant is using an android or iOS (Apple) device. This also allows for the LifeData server to "ping" or alert the participant when a survey is available for completion.

All data collected over WiFi from the smart phone or tablet device is immediately uploaded to the LifeData LLC server based in the United States. Data collected through the use of a data plan

is stored on the phone until the device is connected to WiFi. All data stored on the device of use and LifeData server are encrypted through an Advanced Ecryption Standard (AES) at 256 bit. When data is transferred from the app to the LifeData server, the data is first encrypted using Base64 and then encrypted a second time use AES 256 bit. All surveys are set-up and maintained by designated study staff, protected through role-based security. LifeData, LLC services are similar to that used by the Survey Research Center at Penn State, which we have used in past CATS IRB approved studies.

At baseline and endpoint EMA assessments, parents will complete the DBD-RS,[24] Impairment Rating Scale (IRS) to measure functioning across multiple domains,[26] the Modified Overt Aggression Scale (MOAS)[27] and Inventory of Callous Unemotional Traits[28] to measure aggression, the Affective Reactivity Index[29] as an additional measure of irritability, and the Pittsburgh Side Effects Rating Scale (PSERS) to evaluate side effects.[30] Data collection does not involve public health information (PHI) and is similar to what would be collected through REDcap (study ID and survey responses). Teachers will be sent the DBD-RS and IRS to complete via REDcap at endpoint to measure the effects of treatment at school.

7.2.4 Visits 3-8 (Open label medication trial)

After baseline, participants will begin a 6 to 12-week open label titration of their CNS Stimulant to optimize control of their ADHD symptoms at home. Participants will be evaluated by study physicians every one to two weeks. Study doctors will provide families with prescriptions to fill at their own expense. The IOWA Conners battery used in the phone surveys , IRS and PSERS will be given at each weekly office visit to measure symptom severity, functioning and side effects. Vitals and weight will be measured at each visit. Optimal dose will defined as a tolerable dose leading to best control of symptoms at home using established procedures from our past trials.[11,35] A study MD/PhD level clinician will then complete a CGI Severity Score for ADHD symptoms [37] based on a review of the parent ratings scales - The titration can last less than twelve weeks if optimal dose is found before that and held steady for at least two consecutive weeks (minimum duration three weeks). Resting heart rate, blood pressure and weight will be measured at each visit with height assessed at the first med visit.

7.2.5 Endpoint EMA Assessment (1 week duration)

Once optimal dose is identified, participants will complete a one-week endpoint assessment on their optimal dose with multiple daily ratings of ADHD symptoms and irritability using the same EMA procedures from the baseline to rate behavior on and off the optimized CNS stimulant dose. Dose will not be changed during this week unless a side effect concern arises.

If participants are not able to tolerate CNS stimulants or has less than moderate improvement on CGI-S scale, they will be withdrawn from the study and will be referred back to their treating psychiatrist to discuss about other medication option. These participants will not enter into endpoint EMA assessment.

7.2.6 Visit 9 (Final visit)

Parents will come to complete Pittsburgh Side Effects Rating Scale (PSERS) to evaluate side effects and to return the study material including study provided rating scales.

Due to the COVID pandemic and revised standards for human subjects research, we will hold every other visit through a virtual platform (HIPAA-compliant Zoom or phone) to minimize exposure risk during the open label medication phase. There would be maximum of 4 weeks between assessments in the office, where we will monitor for vitals, weight and height as recommended for CNS stimulants

monitoring (AACP Practice parameters, 2007). Once the pandemic restrictions are lifted, we will return to study procedures (i.e. in-person visits) as described in the rest of the protocol.

7.3 Duration of Participation

Participation in the study will last approximately five to nine weeks, which includes the 2 weeks for EMA data collection and up to 12 weeks of medication trial.

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

7.4.1 Description

The aim of this study is to evaluate if optimization of CNS stimulants reduce irritability in children with ADHD. The medication used in this study will be participants' own CNS stimulants medication, only dose will be adjusted (FDA approved for the treatment of pediatric ADHD and the most extensively studied ADHD medication in children).[45] FDA approved medications for ADHD are - amphetamines (mixed amphetamine salts, dextroamphetamine and lisdesamfetamine – Adderall, Dexedrine, Mydayis and Vyvanse) and methylphenidate and desmethylphenidate (extended and immediate release – Concerta, Daytrana, Aptensio XR, Quillivant XR, Metadate-CD, Metadate-ER, Ritalin LA, Ritalin SR and Focalin or their generic equivalents).

7.4.2 Treatment Regimen

The medication assessment procedure will be open-labeled study. We will use FDA approved doses during CNS stimulants optimization. There will be no blinded medication or placebo as families will be provided with scripts to fill at their own expense, consistent with clinical care.

7.4.3 Method for Assigning Subject to Treatment Groups

N/A

7.4.4 Subject Compliance Monitoring

Medication adherence will be assessed at each study visit by parent report.

7.4.5 Blinding of the Test Article

N/A

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

Study doctors will provide families with prescriptions to fill at their own expense.

7.4.6.2 Storage

N/A

7.4.6.3 Preparation and Dispensing

N/A

7.4.6.4 Return or Destruction of the Test Article

N/A

7.4.6.5 Prior and Concomitant Therapy

Concomitant medicines that are permitted include alpha agonists (clonidine and guanfacine) prescribe for adjunctive control of ADHD in combination with a CNS stimulant will be allowed as the combination is FDA approved. 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.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

The total number of subjects to be accrued is 47.

8.2 Sample size determination

Power analyses were conducted using G-Power version 3.1[60] with a power of .80 and alpha =.05. Aim1 will be examined using a multiple regression with five predictors (age, sex, ADHD severity, delta, theta). A large effect size (effect size f^2 = .35) was assumed, based on prior work reporting a large correlation between RewP and ratings of symptom severity in depression.[17,43] Under these assumptions, a sample size of 43 will achieve an observed power of 0.805. Aim2 will be examined using a mixed model. As there are no clear procedures for determining power and sample size for mixed model analyses, power for a linear regression was used to approximate sample size. A large effect was also assumed for this aim, based on the effects of CNS stimulants on irritability and ERN[12,22,49] and correlations between medication changes in ERPs on the Go/No-Go and parental ratings of behavior.[53,61] A sample size of 43 should be sufficient for this aim. The exploratory 3rd aim will be examined using the same regressions. The association between changes in parent ratings of irritability gathered on vs. off medication has never been formally examined, precluding a precise estimate of effect. It is reasonable to assume such effects would be large given the improvements in irritability with CNS stimulants.[12] Based on our prior work in youth with ADHD and irritability,[11,62] no more than a 10% dropout is predicted, for a total sample of 47.

8.3 Statistical methods

Aim 1 hypothesizes that the amplitude of each ERP will be associated with level of irritability (H1) and that children with elevated amplitudes to both loss and gain will have the most irritability (H2). Associations between ERPs and irritability ratings will be measured by multiple linear regression.
Aim 2 hypothesizes that a smaller ERN amplitude will predict greater improvement. This will be examined by computing a multilevel model with treatment (pre, post) as the level 1 (within subjects) predictor and ERN as the level 2 (between subjects predictor). The hypothesis will be supported if there is an interaction between treatment and ERN. Standard model checking procedures will be used, including checks on distributional assumptions (and transformations as appropriate), collinearity and influential cases.
Exploratory Aim 3 hypothesizes that greater improvement during the day will predict parents rating worsening behavior in the evening as medication effects wane. A multiple regression analysis predicting the change score in irritability ratings collected during unmedicated times from the change score during medicated times will be computed.

9.0 Confidentiality, Privacy and Data Management

9.1 Confidentiality

See Research Data Plan Review Form for this entire section.

10.0 Data and Safety Monitoring Plan

Data collection: EMA data is uploaded directly to a secure server to maximize data retention and accuracy. Additional data will be collected at most visits using electronic forms that load directly into REDCap whenever possible, with paper forms for the rest. All forms will only be labeled with the participant's unique study ID.

Research assistants will enter all of these data points on a rolling basis as the ratings are collected, and check these entries by comparing raw data ratings with computer printouts of the data sets, looking for and correcting any discrepancies. All data will be monitored for accuracy as they are collected by senior research staff, who will immediately contact raters who do not complete questionnaires thoroughly.
Dr. Baweja (PI) 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), Dr. Baweja (or Dr. Waxmonsky if Dr. Baweja is out of town) 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 and weekly during medication trial. 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, side effects of medication using the Pittsburgh Side Effect Rating Scale as well as spontaneous report, vital signs, concomitant medications, levels of ADHD /ODD symptoms and irritability as rated by parents by both EMA and paper measures.

10.3 Method of collection of safety information

Methods of collection of safety information include study visits (parent ratings using EMA) and direct feedback from children.

10.4 Frequency of data collection

Safety data collection starts at the baseline visit. The same parameters will be collected weekly during open label medication trial and end point EMA assessment. 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

10.8 Suspension of research

Study investigators will determine if a discontinuation from the study is appropriate due to any adverse reaction to CNS stimulants. While it is unlikely, as these participants will have had exposure to CNS stimulants, 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.

11.0 Risks

1. Withholding CNS stimulants: Participants (children or family) may become distressed as a result of having to cease current CNS stimulant treatment for one day during the EEG assessment process. Many parents routinely opt not to give medication for a variety of reasons and drug holidays are clinically prescribed to improve weight gain. It is not uncommon for children to intermittently skip or miss medication doses. There is no risk of withdrawal side effects with CNS Stimulants. Participants using alpha agonists will be allowed to continue them as abrupt stoppage could lead to potential side effects easily stopped and there is no evidence they impact ERN or RewP.

2. EEG Risks: Risks associated with participating in the EEG assessment are minimal. Potential risks include boredom or fatigue while completing the computer tasks. There is a possibility of mild skin redness where the EEG electrodes and gel contact the skin; however, this is rare and generally temporary. Participants are assured that they can withdraw from the study at any time if they do not wish to complete the tasks, and participants will be given breaks between EEG tasks to reduce fatigue.

3. Time demands: Participants (children or family) may be 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. Children will receive a $10 gift card for completing lab tasks and parents a $20 gift card for completing each of the two weeks of EMA data collection. Use of ecological momentary assessment greatly reduces the burden to families by avoiding office based visits and shortening the time needed to complete ratings.

4. Distress from answering questions: 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 irritability. They can refuse to answer any questions they are not comfortable with.

5. Side effects of CNS stimulants: It is expected that most participants will already be taking dose of CNS stimulant medications. Our work and others have shown that optimization of CNS stimulant dose in already medicated youth will often improve irritability.[11,63] Only medications FDA approved for pediatric ADHD and only doses within the prescribed FDA ranges will be used. Side effects are not expected to be any different than those seen in routine clinical care. Side effects will be assessed weekly using structured rating scales while medication dose is being adjusted. We will use a structured measure of common CNS stimulant side effects. In addition, families will have 24 hour access to investigator staff should any adverse reactions occur. All physicians working on the study are experienced in the treatment of pediatric ADHD. Dose decreases to address adverse events may be performed at any time. Additionally, Dr. Baweja will review any moderate or severe adverse events within 24 hours. The subject will be contacted (brought back to the clinic if necessary) to make any further medication changes that may be needed. The necessary reports will be filed with the presiding IRB by Dr. Baweja and his staff. Any time parents are concerned about possible side effects during the trial they may telephone the clinic or directly page Dr. Baweja to speak with him about their concerns. All subjects will have access to a 24/7-telephone number to report any of these symptoms or other adverse reactions as well.

   The primary risk to participants includes any potential adverse reactions to the Methylphenidate (MPH) or Amphetamine (AMPH) treatment. The side effect profiles of MPH and AMPH are largely similar with the two medications primarily differing in their potency and duration (Pelham et al, 1999, Greenhill et al, 2002, Cortese 2013). Likewise, rates of side effects are similar amongst the different branded MPH and AMPH preparations. The most common side effects are decreased appetite and weight loss, headache as well as sleep delay, headache. Adverse emotional responses including irritability are also a risk (see below). Uncommon side effects include jitteriness and motor/verbal tics. Rare side effects include visual disturbances, serious cardiovascular problems, raynaud's symptoms, priapism, 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 methylphenidate/amphetamine product. Families will have 24 hour access to investigative staff should any adverse reactions occur.

The medication may also cause an increase in heart rate or blood pressure and can affect seizures in children with existing seizure disorders. Therefore, children with serious heart problems or seizure disorders should not will be determined as ineligible for the study. A study physician will ask subjects if they have experienced any of these problems.

6. Risk of worsening irritability: While most children will experience reduced irritability with adjustment of their CNS stimulant, some may experience an increase especially as it wears off. One of the aims of this study is to examine if this wear off irritability represents a true worsening or just a return to baseline levels. The risk of increased irritability will be reviewed with parents and children during the consent and assent process. The study has multiple measures designed to explicitly assess irritability including two weeks of daily ratings collected by EMA. If there is an increase in irritability, the dose can be adjusted or stopped the same day with no risk of withdrawal side effects. [11,12,65] Participants will be contacted daily until any increase in irritability has resolved.
7. Loss of confidentiality: All test materials will be identified by number rather than name or other identifying information and will be entered into the database only by participant number. The key linking participant names to numbers and identifying information, such as the informed consent forms will be kept on secure server at herhseymed/net. Participants will be instructed not to use full names during the video-recorded parent-child interaction task. EMA measures are uploaded into a secure sever and identified only by study ID number. The EMA methods are designed and supported by the Penn State Survey Research Center to ensure that all data is collected in a secure and timely fashion.

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 persistent irritability 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 CNS stimulants by clinicians who are experts in the management of ADHD, irritability and oppositional behaviors. Children can benefit from this study by displaying improvements in their ADHD and other behavior problems. The information gained from the study may also help parents, clinicians, and educators working with the children with behavioral problems and irritability to develop more effective intervention programs.

12.2 Potential Benefits to Others

Clinical science may gain further understanding about a causal pathway for irritability that will aide treatment development and identified a reliable biomarker for the current first line treatment for irritability in ADHD (CNS Stimulants).

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.

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. Families will be provided with a $10 gift card and prize for completing the single lab-testing day and $20 gift cards for each week of the ecological momentary assessment phase for child appropriate items (Walmart, Toys 'r' Us, Target).

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. EMA surveys may be completed through WiFi or data plan. Standard data rates apply for downloading and using the survey application and incurred data costs will not be reimbursed. 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. Families will be responsible for the cost of filling any prescribed medication, no different than routine care. Study doctors will work with the family to select medication options that are affordable. Most FDA approved ADHD medications come in generic forms or have brand names that are on most major local formularies.

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 subjects 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. Hameed, Dr. Waschbusch, and Dr. Bunce are on faculty at Penn State College of medicine in the Department of Psychiatry while Dr. Khan is a senior resident in Psychiatry at Penn State.

16.2 Feasibility of recruiting the required number of subjects

Participants will be recruited from the Primary care and Psychiatric clinics at Hershey Medical Center in Hershey, PA, which treat over 1400 youth with ADHD, recruiting a total of 47 participants should not be problematic.

16.3 PI Time devoted to conducting the research

1.2 calendar months

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.

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 HRP-902 - Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ 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).

☐ Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901 - Human Body Fluids for Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Clinical Research Center (CRC) Advisory Committee– All campuses – Research involves the use of CRC services in any way.

☐ 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 a copy of HRP-903 - Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ 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

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug

Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

For device studies, incorporate the following definitions into the below responses, as written:	
Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

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.

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

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

N/A

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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