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Application Title: Combined effects of early behavioral intervention and propranolol on ASD

Protocol

1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Finding effective treatments is a primary concern for individuals with autism and their families. Despite decades of research exploring treatment options, few treatments targeting core symptoms of the disorder, such as social communication, exist. Behavioral therapy involving intensive, individualized training is the mainstay of treatment for autism, but drugs targeting autism symptoms can be an important addition to treatment. Explorations of combined treatment approaches, in which drugs are used to augment the effects of behavioral therapy, are limited within the context of autism. Additionally, most currently available drugs target psychiatric symptoms associated with the disorder, including aggression, irritability, and obsessive behaviors, instead of core features.

Previous studies from our laboratory have examined the effects of the beta-blocker propranolol in adults and adolescents with autism. Propranolol inhibits the action of norepinephrine, a brain chemical that drives the stress response, or fight-or-flight, system. Heightened stress and anxiety in autism suggest propranolol as a potentially beneficial drug for this population. Our previous studies have demonstrated a benefit of single doses of propranolol for social functioning, as well as language-related cognitive abilities, in autism. We have also observed that participants with greater levels of stress reactivity demonstrate greater improvements in social functioning with propranolol, suggesting a potential method of predicting treatment response.

In the proposed serial-dose, parallel design study, we plan to explore the effects of propranolol in combination with early intensive behavioral intervention in children with autism. Propranolol or placebo will be administered at the beginning of behavioral intervention sessions in a double-blinded, counterbalanced manner for the course of twelve weeks. Outcome measures will include assessments of social functioning, language, anxiety, adaptive behaviors, and other autism-related symptoms. This study will allow us to examine the effects of propranolol with multiple doses in a trial setting. In addition, this will be the first exploration of this drug's effects in children with autism, an important area of study given the benefits of early intervention. Previous studies involving pediatric migraine suggest that this drug can be used safely in young children. We will also determine whether measures of autonomic nervous system functioning and anxiety can predict which individuals will respond best to the drug. In this manner, we can begin to optimize and individualize combined treatment approaches for treating core symptoms of autism.

2. Objectives (include all primary and secondary objectives)

We propose to examine the effects of propranolol on social interaction in children with autism undergoing early intensive behavioral intervention (EIBI) in a 12-week, double-blinded, placebo-controlled pilot trial. We will also assess the effects of this combined therapeutic approach on language, anxiety, adaptive behaviors, and other autism-related behaviors in these individuals. Lastly, we will investigate how autonomic nervous system (ANS) activity, as measured by heart rate variability and pupillary light reflex, and baseline anxiety might predict the effects of propranolol on social functioning and our other outcome measures. We hypothesize that concomitant administration of propranolol will enhance the clinical benefit made through EIBI by improving social functioning, language, anxiety, adaptive behaviors, and other autism-related behaviors. We predict that this augmentation of EIBI's effects will only be apparent for the propranolol condition of the study. We also expect that ANS activity and anxiety levels will predict response to propranolol on our outcome measures.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Previous studies support the existence of altered noradrenergic activity in ASD, including early studies suggesting increased plasma (1) and urine (2) adrenergic metabolites in autism. Additionally, multiple studies indicate that ASD may be characterized by hyper-restrictive associative networks (3, 4) which may be related to increased noradrenergic signaling (5).These findings suggest the potential benefit of a pharmacological agent aimed at the noradrenergic system for this population. Propranolol, a centrally and peripherally active nonselective beta-adrenergic antagonist, reduces noradrenergic system activity. This anxiolytic has been used off-label for test anxiety (6) and performance anxiety (7) for several decades. Propranolol was first explored within the context of ASD in an uncontrolled case series, which reported improvements in language and sociability (8). Our laboratory has since investigated this agent's effects on a wide range of behaviors known to be affected in ASD, including verbal abilities (9, 10), working memory (11), and facial scanning (12) in single-dose psychopharmacological challenge studies in adults and adolescents with ASD. Most recently, we demonstrated a benefit of a single dose of propranolol on social functioning, assessed via conversational reciprocity, in a sample of 20 high-functioning adults and adolescents with ASD (13). This study also showed a potential association between resting autonomic activity, assessed via heart rate variability, and response to propranolol on the social task. These findings suggest a potential benefit of propranolol on core features of ASD and that treatment response may be predicted by certain markers. Accordingly, further study is necessary to examine if these potential benefits are not only maintained in serial doses, but also if these benefits extend to a younger population of individuals with autism. Behavioral therapy, including early intensive behavioral intervention (EIBI), has been shown to have lasting benefits for social functioning, language, and adaptive functioning in ASD. It has also been shown that behavioral intervention is more beneficial when introduced early in life; therefore, this critical early

stage following diagnosis would be also an opportune time to integrate pharmacological intervention with behavioral therapy to maximize therapeutic benefits.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

The proposed study is a 12-week, parallel design, placebo-controlled pilot trial. For the purposes of this study, we will recruit 30 participants with ASD aged 3-8 who are currently enrolled in an EIBI program. ASD is defined in this study by the DSM-V criteria plus Autism Diagnostic Observation Schedule (ADOS) criteria for Autism. Participants will be screened for this formation as well as inclusion/exclusion criteria to determine their eligibility to participate in this study over the phone prior to obtaining written consent. A waiver of documentation of consent is requested for these screening purposes only. Written consent will be obtained prior to any other study-related procedures. The ADOS may be administered during the initial study visit if a prospective participant does not have ADOS scores from a previous assessment. Additionally, an intellectual assessment (IQ test), the Differential Ability Scales (DAS), may be administered at this time if previous scores do not exist.

Prior to participation in the study, informed consent will be obtained from both parents/legal guardians of the participant, and assent will be obtained from the participant. In addition, the parents and participants will be informed that they can terminate the procedure and exit the study at any time.

We will recruit participants during their participation in the EIBI program at the Thompson Center or other institutions in Missouri. The EIBI team provides one-on-one instruction for individuals with ASD, as they work toward treatment goals of learning new skills and minimizing challenging behavior. EIBI staff will be also be blinded to drug conditions. Given the highly individualized nature of EIBI, each participant's therapy will differ in frequency of sessions per week and length, as well as defined behavioral targets and the methods used to reach them. This variability will be accounted for via a stratified randomization approach (see below) as well as statistically during analyses after study completion.

Upon study enrollment, participants will be randomized to receive either placebo or propranolol for a period of 12 weeks during the study. Drug randomization will be counterbalanced to ensure that half of the participants will receive placebo and the other half will receive propranolol. Randomization will also be double-blinded so that neither participants nor the researchers performing analysis will be aware of the identity of the drug being administered. As participants will be receiving varying levels of intensity of EIBI (number of hours per week), randomization will also be stratified according to different levels of intensity to ensure approximately equal distribution of EIBI intensity between the two drug groups.

The following are brief descriptions of the drugs to be administered:

Propranolol [pro-pran'-o-lol] blocks the brain's and body's use of norepinephrine both centrally and peripherally and also is commonly used to decrease high blood pressure.

Placebo [pla-see'-bo] is a physiologically inactive suspension that looks like other drugs.

Drug administration: Propranolol will be administered in the form of a liquid dose via oral syringe by the participants' parent/caregiver an hour before each EIBI session. Drug administration will begin after the first (baseline) study visit. To minimize risk, the bodyweight adjusted minimum dose of propranolol used safely for test anxiety in healthy adults (10mg) will be used (see table below):

Bodyweight (kg)	Dose (mg)
> 30	4
22.5 - 30	3
15 - 22.5	2
< 15	N/A

This more cautious dosing strategy will be utilized for safety purposes, as children may be less able to report potential side effects. Participants weighing less than 15kg will be excluded for safety reasons.

Heart rate and blood pressure monitoring: Participants with a heart rate of less than 60 or a systolic blood pressure of less than 75 at the outset of the study will be excluded. Heart rate and blood pressure will also be measured via wrist cuff at each study visit. If on any measurement the heart rate or systolic blood pressure is abnormal, the PI will be immediately notified. At this point, the PI may withdraw the participant from the study for safety reasons.

During the study, participants will undergo ANS activity and behavioral assessments (discussed below) at three separate study visits at the following time points: (1) prior to drug administration, for establishment of a baseline (week 0); (2) at approximately week 6; and (3) at the end of week 12. Each study visit is expected to last approximately an hour and half.

ANS Measurements: At each study visit, ANS measurements will be performed to assess autonomic activity. Heart rate variability (HRV), measured via electrocardiogram, will be used to assess sympathetic and parasympathetic nervous system activity. Electrodes will be placed on the chest region in the typical manner, and signal from the electrodes will be amplified by an ECG 100C module connected to a BIOPAC MP150 data acquisition system. Measurements will be recorded for a period of 8 minutes, allowing for 3 minutes of acclimation to the equipment.

We will also evaluate ANS activity via the pupillary light reflex (PLR), a simple functional neurological test measuring pupil constriction and recovery in response to stimulation via a short light flash. During the test, the participant will sit comfortably in a

chair or will be seated on a parent's lap about 1 m from the PLR system. A red-filtered movie will be shown on a projector screen behind the PLR system to attract the participant's attention. During the test, participants' PLR will be assessed in both light- and dark-adapted conditions. A total of 10 trials, each lasting 2.5 sec followed by a 25-30 sec interval, will be performed for each stimulation condition.

Behavioral Assessments: Behavioral tasks and questionnaires will also be performed at each study session. The following assessments will be completed by the participant with ASD:

(1) General Social Outcome Measure (GSOM): The GSOM is a brief evaluation tool that measures a participant's level of social functioning and how it changes with intervention. There GSOM includes 4 different tasks: conversational reciprocity, ability to recognize facial expressions, social problem solving, affect demonstration, and emotional perspective taking. The experimenter administers each component of the GSOM to the participant and then scores their responses according to a pre-determined scoring rubric. Each component is scored on a 1-5 or 0 - 2 scale, with higher total scores indicating better social functioning. A video camera will be used to record the participant's behavior during GSOM administration for the purposes of having two independent raters score the tasks after the study session is complete. The video camera will be turned off for the remainder of the study session. A camera will also be used during the affect demonstration task of the GSOM. Both video recordings and photographs will be anonymized and coded. Parents of the participants will complete a release for video recordings and photographs during the enrollment process.

(2) Preschool Language Scale, fourth edition (PLS-4): To evaluate language, we will administer the PLS-4, which has been developed for use in younger children (birth through age 7), and is appropriate for children of all ability levels, including nonverbal children. This play-based, interactive assessment is designed to assess receptive and expressive language skills and their change over time.

The following assessments/questionnaires will be completed by a parent or caregiver of the participant with ASD:

(1) Comprehensive Review of Systems: At the initial study session only, participants' parents/caregivers will complete a detailed questionnaire about their child's physical and psychological condition, any surgeries or hospitalizations they have had, and any medications they are taking. This questionnaire is for the purpose of maintaining the safety of participants, as the study staff and PI will compare any subsequent symptoms participants report with those listed on this initial review of systems.

(2) Interval Medical History Questionnaire: Participants' parents/caregivers will complete a questionnaire about any side effects their child has experienced since the previous study visit, any new medical or psychiatric diagnoses, and any concomitant medications they are taking or have added since the last study visit, and whether they have visited a doctor's office or hospital since their last study visit. This questionnaire is for the purpose of maintaining the safety of participants, as the study staff and PI

will need to ensure that each participant is not experiencing any adverse events throughout the study.

(3) Demographic questionnaire: A questionnaire ascertaining a participant's personal and family demographic information, such as race/ethnicity, handedness, and socioeconomic status, will be completed by the parent/caregiver at the initial study visit only.

(4) Social Responsiveness Scale, second edition (SRS): This 65-item, parent-report measure asks questions about a participants' social awareness, social information processing, capacity for reciprocal social responses, social anxiety or avoidance, and characteristic autistic preoccupations or traits. Depending on the child's age, the preschool or school-age version of the SRS will be administered.

(5) Clinical Global Impression of Change (CGIC) and Clinical Global Impression of Severity (CGIS) scales: To assess overall changes in the participant's ASD-related clinical symptoms, the CGIC and CGIS will be administered. The CGIC consists of a 7-point subjective scale assessing change from baseline. On this scale, scores of 1, 2, and 3 represent marked, moderate, and mild improvement, respectively. A score of 4 represents no change. Scores of 5, 6, and 7 represent mild, moderate, and marked worsening, respectively. CGIC scores from both the parent/caregiver and a blinded clinician will be utilized. The CGIS is a similar 7-point subjective scale for severity.

(6) Autism Impact Measure (AIM): The AIM will be administered to assess the frequency and impact of a participant's ASD-related symptoms. A parent/caregiver is asked a series of 41 questions regarding the frequency and the impact, or interference resulting from, a series of autism-associated behaviors. Overall impact and frequency scores, as well as subscale scores, will be obtained from this measure.

(7) Vineland Adaptive Behavior Scales-II (VABS): To assess overall adaptive functioning, the VABS will be administered in the form of a structured interview with the parent/caregiver. The VABS is a well validated assessment used for the full range of our subjects' ages and yields standard scores in Communication, Daily Living Skills, Socialization, and Motor Skills. VABS scores for Communication, Daily Living Skills, and Socialization will be monitored in this study.

(8) Aberrant Behavior Checklist (ABC): To assess overall behavioral disturbances, a parent/caregiver of the participants will complete the ABC. This 58-item questionnaire is a well validated, reliable, and widely used assessment tool for interventions for a range of cognitive disorders.

(9) Preschool Anxiety Scale (PAS): To assess anxiety, the PAS will be completed by a parent/caregiver. This 34-item parent-report questionnaire, adapted from the Spence Children's Anxiety Scale (SCAS), yields a total score and five subscale scores based on DSM-IV anxiety disorder structure (separation anxiety, social phobia, obsessive-compulsive disorder, and generalized anxiety), as well as fears related to physical injury.

We will also make efforts to gain the input of participants' parents/caregivers at the outset as well as completion of the study. This will involve the completion of a survey upon study enrollment asking about potential outcomes the parent/caregiver wishes to explore (e.g., gastrointestinal symptoms) in this study. Any suggestions that are not already incorporated to the study and are deemed appropriate and necessary by the PI will

be submitted to the HS IRB as an amendment. Additionally, after completing the study, the participants' parents/caregivers will be asked to complete an exit survey, asking about their child's experience of the study and if they have any suggestions for future studies of a similar nature. This survey will be given to parents/caregivers to complete at the end of the final study visit or mailed when necessary.

We will also make efforts to inform families of the progress of this study via newsletters containing enrollment updates and new (non-study related) findings and news in autism research sent via email on a quarterly basis. Each newsletter will be submitted to the HS IRB for approval prior to being sent out.

b. Study duration and number of study visits required of research participants.

Participation in this study will last 12 weeks and will involve 3 visits to the Thompson Center for Autism & Neurodevelopmental Disorders lasting approximately an hour and a half each. If a private room is not available at the Thompson Center when a participant's visit needs to be scheduled, the visit will take place at the Center for Translational Neuroscience (M741) in the Medical Sciences Building instead.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

This study will be double-blinded for the purposes of removing any bias that could be introduced if either the researchers or the study participants are aware of which drug they are taking at a given time. Blinding of the drugs will be conducted by the University Hospital's Investigational Pharmacy. In the case of emergency, the PI and research staff running study sessions will have access to unblinding information in the form of a sealed envelope.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Routine care for this population will not be affected by this study. Participants will be able to continue routine care, including behavioral therapy or other medications. Potential participants taking medications that are exclusionary for this study will not be enrolled.

e. Justification for inclusion of a placebo or non-treatment group.

A placebo arm of this study will allow for statistical comparisons between behavioral performance for participants who are taking placebo versus propranolol. The parallel design of the trial will involve half of the participants receiving propranolol and the other half receiving placebo. Drug randomization will be counterbalanced.

f. Definition of treatment failure or participant removal criteria.

As this is a pilot trial exploring the effects of propranolol on social and language abilities, there are no behavioral endpoints that we would consider treatment failure. However, for the safety of the participants, if at any measurement taken, a participant's heart rate or blood pressure is abnormal or if the participant is experiencing an adverse reaction to the drug the PI will be immediately notified. At that point, if the PI determines it is necessary, the participant will be instructed to discontinue taking the drug and will be removed from the study.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

When the study ends or if a participant's participation ends prematurely, the participant will no longer take propranolol or placebo. Participants will continue with their routine care as they would have done throughout the study.

5. Inclusion/Exclusion Criteria

Inclusion criteria:

For participants with autism: Individuals with ASD aged 3-8. ASD is defined in this study by the DSM-V criteria plus Autism Diagnostic Observation Schedule (ADOS) criteria for Autism. Participants must also be enrolled in an EIBI program at the Thompson Center or another institution in Missouri for the duration of the study.

For parent/caregiver of participant with autism: Minimum age of 18, no maximum age.

Exclusion criteria:

For participants with autism: Non-autism learning disability (e.g. dyslexia), major psychiatric diagnosis (e.g. major depression, schizophrenia, bipolar disorder), other neurological diagnosis, major head trauma, any of the following exclusionary criteria related to propranolol (diabetes, reactive airway/pulmonary disease, thyroid disease, bradyarrhythmias, unexplained syncope, narrow angle glaucoma, known hypersensitivity/adverse reaction to beta-blockers, potentially interacting drugs, underweight < 15 kg), any of the following exclusionary criteria related to the use of electrocardiogram (history of rash from adhesives), or any of the following exclusionary criteria related to the pupillary response measurement (uncorrectable visual acuity impairment). Participants with a heart rate of less than 60 or a systolic blood pressure of less than 75 at the outset of the study will be excluded.

For parent/caregiver of participant with autism: No exclusionary criteria.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Propranolol is a beta-adrenergic antagonist that dampens the stress response system. Previous studies from our laboratory indicate a potential effect of propranolol on social and language abilities in adults and adolescents with ASD. This pilot trial investigation will explore the effects of serial doses of propranolol in children with autism who are concurrently undergoing EIBI. We predict that propranolol's effects on stress and anxiety will positively impact social and language abilities in children with ASD and augment the effects of EIBI.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Propranolol is part of established care for treating pediatric migraine (14, 15, 16) and infantile hemangioma (17, 18), demonstrating its safety for this population. To

minimize risk, the doses to be used for children in the present study were selected as the bodyweight adjusted minimum dose safely used in otherwise healthy adults for test anxiety. The typical doses for test anxiety in adults (10mg) are lower than those for cardiac indications (starting dose for hypertension is 40mg). Participants taking propranolol in this study may be at risk for the side effects described below. Parents/caregivers and the participants will also be told that there may be other side effects that we cannot predict. Measures to maintain the safety of study participants will be further discussed below. Parents/caregivers of participants will be encouraged to discuss these with the PI (David Q. Beversdorf, MD) and/or their own doctor.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

7. Study Statistics

a. Primary outcome variable.

We are primarily exploring the effects of propranolol on social abilities, as assessed via the GOSM and the SRS.

b. Secondary outcome variables.

Our secondary outcome variables include effects on anxiety (assessed via the PAS), language abilities (assessed via the PLS-4), adaptive/global functioning (assessed via the Vineland), and change in clinical impression/impact of ASD symptoms (assessed via CGIC, CGIS, ABC, and AIM).

c. Statistical plan including sample size justification and interim data analysis.

To determine the appropriate sample size for this study, we conducted a power analysis based on effect size estimates on our previous study examining the effects of propranolol on social functioning in ASD. The power analysis indicated that a sample size of 20 would achieve a proposed power of 0.80 at the significance level of $\alpha = .05$. Behavioral assessments will be compared across study time points and between drugs (propranolol and placebo) using repeated measures multivariate analyses of variance (MANOVAs). We will use simple linear regressions to determine whether variability in baseline autonomic nervous system functioning or anxiety serve as markers to predict treatment response. Interim data analysis will only be conducted for the purposes of presenting preliminary data at academic conferences. The investigational pharmacy will assist in unblinding collected data for these preliminary analyses, keeping investigators blinded throughout the study.

d. Early stopping rules.

As this is a pilot trial exploring the effects of propranolol on social and language abilities, there are no behavioral endpoints that we could consider treatment success or failure prior to the completion of the study, thus we would not stop the study based on early evidence of treatment efficacy or futility. If safety becomes a concern due to side effects associated with propranolol, the PI (in consultation with the HS IRB) may decide

to stop the study early. However, this is not expected to occur given the minimal side effects known to be associated with this drug at these doses.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

The medical risks participants may encounter are those associated with taking the drugs used in this study. Below are the descriptions and side effects associated with each drug:

Propranolol [pro-pran'-o-lol] is commonly used to decrease high blood pressure. This drug can cause problems for persons with depression, diabetes, thyroid disease, very slow heart rates, very low blood pressure, fluid in the lungs from heart failure, and asthma. The side effects related to this drug are given below. These symptoms are most present within 5 hours of the drug administration. None of these symptoms will be present once the single dose is washed out of the system, which can take up to 24 hours.

- Very Likely: Decreased Blood Pressure and/or Slow Heart Rate
- Less Likely: Decreased Sex Drive or Impotence
- Rare: Abdominal Cramps, Diarrhea, Constipation, Fatigue, Depression, Vivid Dreaming and/or Tingling Sensations
- Rare but more Serious Side Effects: Insomnia, Nausea, Hypersensitivity/Allergy, Dizziness, Drowsiness or Lightheadedness, Very Slow or Uneven Heartbeats, Swelling of Ankles/Feet and/or Difficulty Breathing

Placebo [pla-see'-bo] is a physiologically inactive suspension that looks like other drugs. The placebo doses will not have any risk associated with their administration.

Participants may also encounter minor risks associated with the adhesives used to collect ANS data via electrocardiogram. Participants may develop a small rash where the sensors attach to their chest. If this occurs, the rash normally subsides shortly after the study visit. Participants and their parents/caregivers will be asked to notify a member of the study staff or the PI if the rash persists.

There are also psychological risks of boredom and probing for personal and/or sensitive information in the tasks and questionnaires the participants will complete as part of this study.

There is the potential risk of a loss of privacy, in which information related to participants' autism diagnosis and their answers to the tasks and questionnaires being administered will be obtained.

b. Steps taken to minimize the risks.

Strict adherence to the exclusionary criteria of this study will minimize the chance of enrolling participants who might be put at risk by taking propranolol. Before enrollment in the study, the PI (a licensed physician) will meet in person with prospective

participants and their parents/caregivers to evaluate their ability to safely take part in this study. Upon enrollment in the study, participants' parent/caregiver will be given a business card containing contact information for lead study staff and the PI in case of questions and/or emergency. Additionally, one week after the initiation of drug administration (at approximately week 1), a member of the study staff will call the participants' parents/caregiver to inquire about any possible side effects associated with the drug (listed above). Any reports of adverse response to the drug will be communicated to the study PI.

Given the chance of unforeseen side effects associated with the drug in participants who met criteria for participating in the study, monitoring of heart rate and blood pressure will occur at each of three study visits. If on any measurement the heart rate or systolic blood pressure is abnormal, the PI will be immediately notified. At this point, the PI may withdraw the participant from the study for safety reasons. Participants with a heart rate of less than 60 or a systolic blood pressure of less than 75 at the outset of the study will be excluded.

At each study visit taking place at the Thompson Center for Autism & Neurodevelopmental Disorders or the Center for Translational Neuroscience, a member of the study staff will first confirm with the participant and his/her parent/caregiver that no changes in the participant's physical condition have occurred since he/she met with the PI in person. A medical and pharmaceutical history will also be obtained to ensure the participant's condition has not changed in a way that would increase the risk of taking propranolol. Any new symptoms or diagnoses will be reported to the PI, who will follow-up with the participant and parent/caregiver if necessary.

Participants with previously documented history of rash from adhesives will be excluded from the study. This will minimize the risks associated with the ANS measurements taken during the study sessions.

To minimize the risk of boredom, participants will be given the opportunity to take breaks and ask any questions they have.

To minimize the risk of probing for personal and/or sensitive information, testing will take place in a private room at the Thompson Center. If participants have difficulty with disclosure of information on some surveys, they will be reminded that their answers will be kept securely and are confidential.

To minimize the risk of loss of privacy, the data will be coded, password-protected, and stored separately from the consent and screening forms in a locked filing cabinet. However, in the unfortunate event that a loss of privacy occurs, it is possible that information related to a participant's autism diagnosis and performance on the tests being administered will be obtained.

c. Plan for reporting unanticipated problems or study deviations.

   Any unanticipated problems or study deviations will be immediately reported to the PI and HS IRB via an Event Report for further investigation.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

   The risk of loss of privacy is minimized as the data will be coded, password-protected, and stored separately from the consent and screening forms in a locked filing cabinet. However, in the unfortunate event that a loss of privacy occurs, it is

possible that information related to a participant's autism diagnosis and performance on the tests being administered will be obtained.

e. Financial risks to the participants.

There are no expected financial risks associated with this study. However, in the event of an injury associated with the study, participants may be responsible for paying for medical expenses associated with that injury. This determination would be made in consultation with the University of Missouri Risk Management Officer.

9. Benefits

a. Description of the probable benefits for the participant and for society.

It is possible that participants may experience benefit on the behavioral assessments of social functioning, language abilities, anxiety, and global and adaptive functioning in the propranolol condition. Otherwise, there are no direct benefits to the participant. If propranolol is shown to improve ASD-related symptoms, with the greatest benefits being for those with the greatest dysregulation in autonomic activity, propranolol may be used to treat others with similar conditions.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Participants will be compensated $25.00 for each completed study visit they complete, for a total of $75.00 if they complete all three study visits. Furthermore, participants will be compensated $25.00 for diagnostic testing, if needed, via the Autism Diagnostic Observation Schedule (ADOS) and $25.00 for IQ testing, if needed, via the Differential Ability Scales (DAS). If a participant lives more than 50 miles from Columbia, MO, the family will be eligible for a flat rate of $75 per visit to offset of costs of travel to the Thompson Center. If a family is eligible for travel funds, they could be paid a maximum of $225 for travel-related expenses. Payments will be mailed in the form of a check within approximately one month after each study visit.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

All test procedures, materials, and medications are paid for by the study. The only expected direct cost to the participants will be transportation to and from the Thompson Center for Autism & Neurodevelopmental Disorders or Center for Translational Neuroscience if the family lives within 50 miles of Columbia, MO. Participants' parents/caregivers may also be responsible for costs incurred in the research for ancillary resources, such as medical treatment, psychological counseling, emergency services or concomitant medications.

12. References

a. List of references supporting research question.

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