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OF NEW JERSEY

RESEARCH PROTOCOL

STUDY INFORMATION

- **Title of Project:**
  A Pilot/Feasibility Study of the Use of High Dose Propranolol to Treat Severe and Chronic Challenging Behaviors in Adolescents and Adults with Autism Spectrum Disorders

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1.0 Research Introduction
1.1 Purpose/Specific Aims

Severe challenging behaviors such as aggression and self-injury can cause significant morbidity and decrease the quality of life for individuals with Autism Spectrum Disorders (ASD). The prevalence of these symptoms varies according to patient samples however one study has placed it as high as 68% (Kanne & Mazurek, 2011). The mainstay of medical treatment for significant aggression in individuals with ASD are antipsychotics. However, as many as 40% of individuals can be resistant to any pharmacological treatment (Adler et al., 2015). Inadequate treatment necessitates the use of physical force, take down and four-point restraint making the improved treatment for this group acute (Van Schalkwyk et al., 2015). Without proper treatment, individuals face severe injuries (retinal detachments, tooth loss, concussions, infections, hospitalizations), and potentially jeopardize school placements, vocational training and/or residential placements.

There are only two medications (Risperdal and Abilify) rigorously studied and FDA-approved for the treatment of irritability in individuals with ASD. These medications are not always successful and have many short and long-term side effects making their use problematic even in cases where the behavioral outcome is successful (Orsolini et al., 2016). Well-designed studies demonstrating efficacy and safety of alternative medication treatment choices for this population are needed.

There is preliminary evidence that high dose propranolol can be effective in individuals with ASD who display severe aggression and have not responded to antipsychotics or mood stabilizers. Concerns regarding the safety of high dose propranolol have limited its clinical application. Well-designed clinical trials demonstrating the efficacy and safety of high dose propranolol will have significant effects on clinical practice and improve the physical and behavioral quality of life for an underserved subset of individuals with ASD.

Our current proposal will pilot the safety and efficacy of high dose propranolol. We will randomly assign participants to either propranolol or to placebo later crossing each participant over to the other group. As propranolol can cause changes in blood pressure and heart function, each participant will complete initial comprehensive testing to monitor cardiac safety throughout the study. We will be utilizing telemedicine and computer based telemetry to minimize the burden of office visits on the individual and family.

A. Objectives
Aim #1: To demonstrate the feasibility of treating and evaluating severely behaviorally impaired participants with aggression, self-injury, and disruptive behaviors who are diagnosed with ASD, using high dose propranolol to obtain blinded randomized placebo controlled data.

Aim #2: To document the cardiac effects of various dosing levels of propranolol through careful follow up of blood pressure/heart rate (BP/HR) and repeated Holter monitoring to ensure the safety of using these doses.

Aim #3: To evaluate and analyze the sensitivity and specificity of the secondary dependent measures of challenging behaviors in order to develop novel and innovative data collection methods of studying this population. These novel methods will be used to develop more rigorous and adequately powered studies in the future.

B. Hypotheses / Research Question(s)

Hypothesis #1- High dose propranolol will show evidence of being effective in treating the symptoms of aggression, self-injurious behaviors and disruptive behaviors, defined as greater than a 25% reduction in the Aberrant Behavior Checklist—Community (ABC-C) Irritability subscale and a rating of much improved or very much improved on the CGI-I scale.

Based on the literature and the results of our preliminary data, we anticipate that propranolol will be an effective treatment for these challenging behaviors. It would be optimal to do this as part of a formal clinical trial powered to give statistical significance; however, this would be possible in this application only if the effect size is very large. At this point, a pilot grant to obtain needed data is scientifically more appropriate. Our pilot will address the preliminary questions and gather the data needed to design a larger, more costly, clinical trial. Some of the preliminary information needed includes: 1) whether there is an optimal target dose of propranolol, 2) the extent of the improvement of challenging behavior which can inform us as to how to power a larger study, and 3) reliability and validity of rating instruments which are targeted to the symptoms we are focused on in this study (i.e. a more sensitive measure of improvement).

This study is designed to address important questions about propranolol at the level of the individual participant. We will be able to review clinical information on the effects of propranolol in adolescents and adults with ASD and challenging behaviors. We will be able to monitor our ability to recruit and retain such participants as well as our ability to obtain the cardiac clearance and safety cardiac monitoring. We will be able to review the tolerability of our stepwise increase in the study medication as well as document the changes in behavioral function in the study participants. The purpose of the crossover design is to use each participant as a control, which is important in ensuring that behavioral changes are not due to placebo effect.

Hypothesis #2- We hypothesize based on our preliminary data that the propranolol will not necessitate discontinuation of the medication in nearly all cases.

On high doses of propranolol (daily dose of 240 mg or more), there will be a decrease in heart rate and blood pressure; however, we will carefully monitor all changes with a set of acceptable cutoffs as well as through clinical evaluation by the cardiologist. We will utilize cutoff scores for pulse and blood pressure (BP < 90/50 and HR < 50 or clinical symptoms of significant dizziness or fainting or near fainting) with these findings necessitating discontinuation of treatment. Holter monitor exam showing any clinically significant changes will also be grounds for discontinuation at the discretion of the cardiologist.

Propranolol has been used on a worldwide basis for over 50 years. It has proven to be a very safe medication with side effects well known. One proviso, however, is that there is a lack of safety data in the literature with the use of high doses. Based on our pilot study including about 30 Holter monitor exams, we did not observe problems with high doses as there were no changes other than the expected drop in pulse and blood pressure. For this research project, we include diligent monitoring of the cardiac status of our participants which includes not only a comprehensive baseline cardiac assessment (cardiac clearance) but also repeated heart rate and blood pressure monitoring to be obtained remotely and available to the research team through telemetry. We anticipate a drop in blood pressure and pulse with increase dosage and we will include these parameters in determining the rate of titration and therefore do not anticipate that participants will drop out due to clinical concerns. We do not anticipate there will be significant cardiac changes as the dose increase as it is likely that peripheral receptors will be saturated and the higher doses will have mostly an enhanced behavioral effect. This will be documented with our monitoring and Holter monitor.

We will utilize Holter monitoring to ensure participant cardiac safety (Aim #2). This type of monitoring will also allow us to capture data on heart rate variability (HRV), which has been used as a proxy for autonomic functioning. Although our study is not designed to answer questions of the mechanism by which the effect of propranolol might be working, one possible hypothesis is that its mechanism is through blocking of sympathetic neural activity. We will be able to examine the HRV measure prior to the introduction of the treatment medication and then at various doses. We will examine whether the baseline HRV predicts improvement on propranolol. If so, HRV could be an inclusion criterion for future studies.

1.2 Research Significance

The ASDs are a heterogeneous group of disorders with multiple etiologies and pathophysiologies and myriad of behavioral symptom presentations (London, 2014; Waterhouse & Gillberg, 2014). It is very likely that to be effective, treatment regimens will have to account for this heterogeneity. A unitary treatment for ASD is unlikely. Rather, the optimal management of ASD and especially the severe symptoms often associated are thought to be multimodal, including both behavioral and pharmacologic intervention (McDougle, Stigler, & Posey, 2003) and must be specific to the symptoms found in each individual.

Although the “core signs” of ASD comprises social deficits and rigid repetitive behaviors, many individuals with ASD have comorbid behavioral symptoms including tantrums, aggression self-injury, hyperactivity, anxiety, rapid changes in mood and others (Lecavalier, 2006). These symptoms, especially the most severe

among them (aggression, self-injurious behaviors and disruptive behaviors), are a common chief complaint of parents and educators and at times far outweigh the core signs as problems (Carroll et al., 2014; Lecavalier, Leone, & Wiltz, 2006; Matson & Jang, 2014). The prevalence of these symptoms in ASD cases varies according to the patient samples studied however one report places it as high as 68% (Carroll et al., 2014; Kanne & Mazurek, 2011). Presently, the treatments for these symptoms continue to yield only partial benefit for many. Two antipsychotic medications, Risperdal and Abilify, are the only two medications which are FDA-approved for the treatment of ASD, more specifically, for the "irritability (tantrums, aggression and self-injury) associated with autism". While very successful for some, their efficacy is far from optimal with one study showing 40% of the sample being resistant to any pharmacotherapy (Adler et al., 2015).

Further, these medications are associated with many adverse effects making their long-term use problematic in many cases (Orsolini et al., 2016). Antipsychotics, used to treat various pediatric CNS disorders are associated with three times the risk of diabetes with these effects observed within one year of follow-up (Bobo et al., 2013). Pediatric patients also gain a significant amount of weight, notably, as much as 7% increase in weight in 12 weeks under antipsychotic treatment (Correll et al., 2009). The need for improved treatment of these symptoms is acute. Often inadequate treatments necessitate the use of physical interventions, takedowns and four-point restraint (Van Schalkwyk et al., 2015) and can disrupt typical family life for the parents and siblings of these individuals.

Behavioral treatments for aggression and self-injurious behaviors have been successfully employed for many years. Perhaps the main limitations of using behavioral methods are those caused by an inadequate number of practitioners with the knowledge and ability to implement these strategies (Van Schalkwyk et al., 2015) as well as the cost associated with intensive treatment. Even if the service delivery systems are optimal however, there are limitations that come along with using behavioral methods alone. Behavioral methods are based on cause-effect relationships and the treatment is accomplished by altering the environmental component of the relationship (Iwata & Dozier, 2008). However, 25% of individuals with self-injurious behaviors are found on functional behavior analysis to have "automatic reinforcement." In other words, the problem behavior was not displayed in response to any demonstrable environmental condition (Hagopian, Rooker, & Zarcone, 2015). Rather, automatically reinforced, sensory-maintained behaviors are thought to be self-reinforcing, and therefore internal biologic functions are likely to be driving the behavior. Because a problem behavior may also serve multiple functions, the behavior may be facilitated, at least in part, by the biological underpinnings of that individual. This conclusion would imply that combination of treatments would be synergistic, and therefore, superior.

Broader, public health issues also need to be considered. There are high levels of psychiatric hospitalization in this population, with 10.8% of children with ASD having had a hospitalization, most commonly for self-injurious behaviors or aggression (Mandell, 2008). Medicaid expenditures are ten times higher for those diagnosed with ASD compared to other children, with the difference largely attributable to inpatient psychiatric care (Mandell, Cao, Ittenbach, & Pinto-Martin, 2006). As the children age, the expenditure for these behavioral symptoms increase and there is a concomitant decrease in the

expenditure for other services which are more consistent with medical home aspirations and life skills (Cidav, Lawer, Marcus, & Mandell, 2013; Mandell et al., 2006). Therefore, large amounts of the resources devoted to ASD go to the management of those with these severe symptoms at the expense of other less emergent but necessary goals.

In the literature, well designed studies for the serious challenging behaviors associated with ASD are scarce. There has been however, many anecdotal or small case series reports which show some promise. One of these strategies involves the beta-adrenergic blocking agent propranolol. The literature on the use of propranolol for these symptoms (in a variety of psychiatric disorders), suffers from various limitations. Most of the literature is made up of case studies although there have been six small double-blind and/or placebo controlled studies (Ruedrich & Erhardt, 1999) involving patients with these symptoms. Although treating aggression, self-injurious and destructive behaviors is common to all six studies, they involved many different psychiatric diagnoses, including intermittent explosive disorder (with and without known brain damage), conduct disorders, attention deficit disorder, schizophrenia, atypical psychosis, schizoaffective disorder, drug abuse, seizure disorder, borderline personality disorder, various types of intellectual disabilities with various etiologic origins and dementia (Jenkins & Maruta, 1987; Silver et al., 1999; Ward, Tharian, Roy, Deb, & Unwin, 2013). Some studies used mixed diagnostic populations. The studies were done on a wide range of ages from children to geriatric cases and over a wide range of IQ's.

Specifically, for ASD, in 1987 a case series of 8 adults with violent or self-injurious behaviors was reported (Ratey et al., 1987). The authors described a "remarkable" effect on previously intractable aggressive behavior which was consistent with similar findings in the studies involving individuals diagnosed with schizophrenia, brain damage and severe mental retardation. In a recent review of the effect of beta adrenergic blockers on behaviors of people with developmental disability, it was reported that many had positive outcomes and supported the efficacy for this indication, despite the overall quality of the research being poor with no randomized controlled studies have been performed (Ward et al., 2013). In a review of studies on brain injured patients with aggression (Fleminger, Greenwood, & Oliver, 2006), it was concluded that beta blockers have the best evidence for efficacy of all medications while these authors also highlighted the lack of quality studies.

Despite the urgent need for treatment for these debilitating symptoms, and the anecdotal success propranolol has had for aggression treatment across a range of diagnoses, it appears that it is not commonly used for ASD treatment. In the UK, adrenergic blocking agents are rarely prescribed, with only 2% of patients with ASD receiving any type of beta blockers (Murray et al., 2014). In a study of pharmacologic treatments in Germany, no beta blockers were listed in the most common 25 medications prescribed for ASD (Bachmann, Manthey, Kamp-Becker, Glaeske, & Hoffmann, 2013). In systematic reviews of treatments for ASD propranolol is either not mentioned or is briefly mentioned in the context of there being no high-quality studies to demonstrate its efficacy (Baribeau & Anagnostou, 2014; Siegel & Beaulieu, 2012).

1.3 Research Design and Methods

This is a randomized, double blind, placebo controlled crossover study. Participants will include individuals with ASD between the ages 12-30. Based on the gender distribution of ASD in the population, we expect that our group will be approximately 75% male. Participants will be recruited from the local New Jersey community, including schools, work programs, and parent support groups.

a) *Randomized*: the researchers will not decide which group the participant will be assigned. The assignment to group A (propranolol first) or group B (placebo first) will be determined by chance and recorded by the research pharmacist.

b) *Double-blind*: the researchers, the study staff, and even the participant and his/her family *will not know* what kind of treatment is provided first or what phase they are in during the study. They will be unblinded at the end of the study, as well as during the open-label study.

c) *Placebo-controlled*: an identical-looking inactive drug ("sugar pill") will be compared to propranolol to account for variables such as improvements related to simply knowing that one is receiving a treatment, attention from researchers, and the expectations of drug's effectiveness by the research team and the caregivers.

d) *Cross-over*: the participant's initial assignment to a particular group (A or B) will be *switched* to the other treatment phase (A → B *or* B → A) after a washout period. That is, each participant will receive a sequence of both propranolol and placebo. In crossover design, the influence of confounding covariates is reduced because each participant serves as his or her own control.

Inclusion Criteria

1. Males and females between the ages of 12-30 years.
2. Diagnosis of ASD conducted by a clinician with confirmation using ADOS or SCQ
3. **At least one of the following challenging behaviors**
   a. Self-injurious behaviors (e.g., hitting one's self, head banging or banging of other body parts causing some degree of tissue damage);
   b. Physical aggression towards others (e.g., hitting, kicking, pushing, spitting or throwing objects at others);
   c. Disruptive behaviors including property destruction during anger episodes, excessive screaming which interferes with functioning

   AND d. The challenging behaviors are generally (but not necessarily exclusively) associated with a congruent affect (i.e. anger or rage when aggressing) as determined by the study psychiatrist.
4. Pharmacologic treatment with at least two psychotropic including one antipsychotic medication has yielded inadequate outcome (partial improvement on one or more medications is acceptable for the study).
5. Clinical Global Impression Severity scale (CGI-S) score of 6 or 7 (severely impaired or most severely impaired).
6. Aberrant Behavior Checklist--Community (ABC-C) Irritability scale score at or above 18.

7. Medical and cardiac clearance.

Exclusion Criteria

1. Asthma or any history of asthma or any disorder involving bronchoconstriction
2. Cardiac Diseases in which the use of propranolol at high doses would be contraindicated.
3. Uncontrolled Seizure disorder (seizure free for > 1 year and no changes in seizure medication in the previous six months).
4. Diabetes or a history of ketoacidosis.
5. Any other medical disorder or medication which would contraindicate the use of propranolol.
6. History or allergy or adverse reaction to propranolol.
7. Pregnancy.
8. Medication exclusions include clonidine/guanfacine / methylphenidate or dexamphetamine l (or similar ADHD medications/ digoxin or other medications affecting blood pressure.

1.3 A. STUDY PROCEDURES

1.3 A1 PRE-ENROLLMENT

- An independent Data and Safety Monitoring Board (DSMB) will be established to ensure the safety of research participants and the integrity of the study data. The DSMB will meet prior to the enrollment of the first participant to review the research protocol, informed consent, and plans for safety and data monitoring of the study. This review is to determine the risks and benefits to research participants, protection and safety of the participants, and to offer suggestions for improving the study (**see SAFETY section for further details).**
- **Participant Screening and Consent and Diagnostic Confirmation-**
  - Upon referral, the study staff will contact the referring person by telephone to get preliminary information as to whether the individual meets **inclusion criteria.** We expect about 25% of those screened to be candidates for a propranolol trial. Therefore, we may need to screen 80 referrals in two years to find 24 eligible subjects. If the initial screening telephone call is successful, an appointment will be made for an initial visit in the Children's Health Institute.
  - At the initial study visit, the research Coordinator/ PI will describe the study in detail with the family (see consent procedures) Informed consent will be obtained by the Research Coordinator. Confidentiality will be protected by assigning a study ID with (no identifying information) for each participant and all information obtained on each participant will be referenced through their study ID.
  - Diagnostic confirmation of an ASD diagnosis.

- **Cardiac Clearance**:
  An appointment will be made for a complete cardiac exam by the pediatric cardiology team in the Clinical Academic Building at Robert Wood Johnson Medical School. This will include a

full cardiac physical exam including history review, vital signs, auscultation, and circulatory assessment. A baseline EKG will be completed (and reviewed by the cardiologist) to detect arrhythmias or heart block that might be an exclusion for participation in the study. A limited echocardiogram will be completed to assess cardiac functioning. The participant will be fitted with a portable 24-hour Holter monitor. The results will be transmitted to the cardiology department and reviewed by the cardiologist. After review of all these tests, our Co Investigator, Dr. Gaffney, will notify the PI or RC regarding eligibility into the study. If our cardiac exam uncovers an unknown cardiac problem, the PI will discuss the findings with the subject's family and Primary Care Physician to ensure the subject receives referral for further treatment. Dr. Gaffney will discuss with the family and PCP if additional testing/clinical follow-up is needed. The family and PCP may decide to follow-up at RWJ cardiology or may choose another provider. The participant will however, not be enrolled in the enrollment study arm without clearance from cardiology. (Before the appointment with cardiology all female participants will take a urine pregnancy test. A negative urine pregnancy test will allow further participation.)

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1.3 A2 ENROLLMENT

Baseline Behavior

- Once the prescreening is complete and subject remains eligible, the subject will be enrolled in the active study. The study coordinator will meet with the family to train them on the use of the home blood pressure and heart rate monitoring. The family will receive a smart tablet to record behavioral questionnaires and medical data. This tablet will collect data through HIPAA-compliant web application. The study coordinator will train the family to use the study tablet and the internet, as necessary.

- The blood pressure readings will be collected by the family and electronically transmitted to the study staff. The family will not be blind to the measurement outcome. These data will be monitored by the study coordinator.

A 2-week baseline period will be begin once admitted to the active study. During the Baseline period, demographic data will be obtained using the *Vineland-3* to assess the adaptive behaviors and IQ (if not available from the previous three years, we will administer the *Leiter International Performance Scale, Third Edition* (Leiter-3). The *Questions About Behavior Function* (QABF) will be administered to assess whether the participant's challenging behavior serves a clear function.

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Randomization and Medication Dispense

The Rutgers Research Pharmacy will supply active study drug and placebo at the first treatment visit. Prior to dispensing the study drug, the participant will be randomly assigned to propranolol

(Phase A) or placebo (Phase B). *All participants will remain on their pre-study medication throughout all phases of the study.

- **Titration Phase** -. *All participants will remain on their pre-study medication.

a) The standard dosing of propranolol will be 10 mg tid (3 times per day), 40 mg tid, 80 mg tid, 120 mg tid, 160 mg tid and 200 mg tid (PHASE A) or matching placebo (PHASE B).
b) All patients will begin at dose one (10 mg tid or 30 mg per day of propranolol/placebo). The family will obtain HR/BP readings on the first 3 days (1 hour after evening dose) after beginning study drug and for the first three days of each dose increase. The HR/BP readings will be transmitted to the RA/PI to review as per safety guidelines (see below).
c) Each week the family will complete behavioral data online through RedCap (Side Effects Survey, Aberrant Behavior Checklist--Community (ABC-C), Questions About Behavior Function (QABF), IBR Modified Overt Behavior Scale (MOAS). Each family will be emailed a link which opens to a behavioral form with subject ID and no identifiers. Once the form is completed by the family member, it is automatically uploaded to the RedCap database.
d) The study psychiatrist will utilize two-way teleconferencing (i.e., Skype-like HIPAA-approved platform) to conduct study visits with the participant and his/her family.
e) There will be weekly follow up with the study psychiatrist, participant and family to review the behavior of the participant. The study psychiatrist will complete CGI and review the Side Effects survey, the ABC, QABF, RBS and IBR modified and titrate up in stepwise fashion based on weekly follow up visits with the study psychiatrist
f) The dose will be titrated up in stepwise fashion (based on the weekly follow up visits) until adequate therapeutic response is obtained (as decided by the subject's/subjects parents and study psychiatrist) or up to a maximum dose of 600 mg per day (note: propranolol is FDA-approved up to a dose of 640 mg).
g) The dose can be raised as frequently as once per week. The titration schedule however will be flexible and the dose can be held steady for an extended period primarily if it is deemed that additional observation is needed prior to increasing the dose.
h) Scheduled dose increases could be delayed due to mild adverse effects (i.e. some nausea, tiredness or difficulty adjusting to medication or parent preference) or due to marked improvement at a lower dose. Dose reduction to manage side effects are allowed at any time.
i) **OPTIMAL DOSE PHASE-** If the dose is held steady for 6-8 weeks, due to optimal behavioral outcome, that will be considered the maintenance dose.

- **CROSSOVER PHASE** *All participants will remain on their pre-study medication.

WASHOUT -

The study drug (placebo or propranolol) will be decreased approximately every three days until no study drug.

The downward titration schedule can be slower, depending on clinical factors (although this was not needed in our preliminary study--London et al., under review).

SWITCH

Participants who were in Phase A switch to Phase B

Participants who were in Phase B switch to Phase A

OPTIMAL DOSE PHASE - If the dose is held steady for 6-8 weeks, due to optimal behavioral outcome, that will be considered to the maintenance dose.

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- **OPEN LABEL** *All participants will remain on their pre-study medication.
  a) After completing the crossover study, all participants will be invited to participate in an open label study on propranolol.
  b) The "double blind" will be broken and the psychiatrist with the parent or guardian will evaluate whether there was benefit on active medication and which dose was optimal.
  c) Participants will be offered the opportunity to again be titrated to the optimal dose for two months.

All participants, whether or not they complete the double blind portion of the study, will be eligible for the open label study. We anticipate **that** ***participants may be more likely to drop out of the double blind during placebo portion of the study (due to delays in treatment with the study drug and continued behavioral difficulties) or during the crossover phase when on study drug (due to decrease in optimal dose of study drug and increase in behavioral difficulties).***

TABLE 1.3 STUDY PROCEDURE – table with all research procedures being performed, when and where they are performed, and by whom.

Procedure						Phase A								Phase B							
	Evaluator	Frequency	Duration (min)	Pre-enrollment	2-wk Baseline	Dose 1: 30 mg	Dose 2: 120 mg	Dose 3: 240 mg	Dose 4: 360 mg	Dose 5: 480 mg	Dose 6: 600 mg	6-wk Maintenance	Washout & Crossover	Dose 1: 30 mg	Dose 2: 120 mg	Dose 3: 240 mg	Dose 4: 360 mg	Dose 5: 480 mg	Dose 6: 600 mg	6-wk Maintenance	Open Label
Consent to participate	Staff	1x	60	x																	
Medical & psychiatric history	GF,BZ,EL	1x	20	x																	
Record review, family & treatment Hx	EL,BZ	1x	30	x																	
Diagnostic confirmation / IQ / CGI-S	EL,BZ,HY	1x	90	x																	
Parent training on vitals	RN	1x	40	x	x																
Vitals (HR and BP)	RN/Parent	W*	5	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Cardiac clearance	JG	1x	90		x																
Holter monitor, HRV	JG	5 total	>6 hr		x			x				x				x				x	
Randomization	Pharm	1x	--		x																
Medication Dispense & delivery	Pharm	W	--			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Clinical Visit	EL	W	20		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Side effects survey	RN,EL	W	5		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CGI-I	EL	W	5		x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x
Vineland-3	Parent	2 total	60		x																x
Aberrant Behavior Checklist	Parent	W	15		x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x
Questions About Behavioral Function	Parent	W	10		x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x
IBR Modified Overt Aggression Scale	Parent	W	20		x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x
Behavior management consultation	HY	1x	60			Upon study completion or termination															

Pharm= Pharmacy; RN =Research Nurse; BZ = Barbie Zimmerman-Bier; EL = Eric London; JG = Joseph Gaffney; HY = Helen Yoo;
1x = once; W = weekly

The pre-enrollment phase, baseline, and the initial study visit with cardiac clearance- which will occur in the Child Health Institute and Pediatric Cardiology sites.

Once enrolled, the weekly study visits will occur via teleconferencing. The study psychiatrist will utilize telemedicine (i.e., HIPAA-approved platform) to conduct study visits with the participant and his/her family. This will circumvent some of the difficulties in having aggressive participants with developmental disabilities attend outpatient clinics, which tend to exacerbate their symptoms.

1.3 B What data points will be collected including long-term follow-up?

Following the pre-enrollment phase, all behavioral data (i.e., questionnaires) will be completed online through RedCap. Each participant will be emailed a link which opens to a behavioral form with subject ID and no identifiers. Once the form is completed by the family member, it is automatically uploaded to the RedCap database. The family will be provided with training on how to complete the questionnaires and to collect vitals prior to beginning data collection. These include:

- *Side Effects Survey*
- *Aberrant Behavior Checklist--Community (ABC-C)*
- *Questions About Behavior Function (QABF)*
- *IBR Modified Overt Behavior Scale (MOAS)*

Data will be collected at predetermined points (see above chart). No long-term follow-up is planned beyond the open-label trial.

1.3 C Define the duration of the study and the length of time each subject will participate in the study.

The study will be 5-7 months long. Each participant's duration of participation will vary depending on his/her response to the medication. That is, based on the participant's clinical presentation, the blind investigator may shorten or lengthen the duration of a particular dosage.

1.3 D. Describe any primary and secondary study or safety endpoints

Primary Endpoint
The primary efficacy parameter will be the change from baseline to endpoint of the double-blind phase. The end-point is the last non-missing, post-baseline assessment of the double-blind phase.

The efficacy will be measured by the ABC-Irritability Subscale, which is rated by the parent or primary caregiver.

Secondary Endpoints

- Change from baseline on the ABC-Irritability Subscale at other time points of the double-blind phase and the open-label extension phase.
- Change from baseline on the other ABC subscales (Lethargy/Social Withdrawal, Stereotypic Behavior, Hyperactivity/Non-compliance, and Inappropriate Speech) at each visit and end point during the double-blind phase and the open-label extension phase.
- Change from baseline at each visit and to end point (last non-missing, post-baseline assessment) in CGI-S during the double-blind phase and the open-label phase.
- Percentage of subjects with CGI-C ratings of "much improved" or "very much improved" at end point (last non-missing, post-baseline assessment) of the double-blind and open-label phases.
- Response rate at each visit; with response defined as at least 25% improvement in ABC-I from baseline.

1.4 Preliminary Data

Our group has obtained a retrospective case series with n=46 patients (38 males, 8 females), which is currently under editorial review (London, Fethke, Zimmerman-Bier, & Yoo). The mean age of the patients was 16 years (range = 8 to 32 years). The mean propranolol dose was 462 mg per day (range = 120 mg to 960 mg). The mean dosage for males was 481 mg (range = 120 - 960 mg) and for females was 372 mg (range = 120 - 640 mg). Twenty-five of the 46 patients engaged in self-injurious behaviors while the remaining patients engaged in various aggressive behaviors. The time on propranolol ranged from 0.1 year (one patient who deteriorated on propranolol also discontinued their antipsychotic at the same time) to 10 years on propranolol with the average duration on propranolol being 2.6 years. The mean number of medications previously and or currently being tried was 6.2 and the number of previous medication trials varied from 1 - 17 different medications.

Our results show that 39 (85%) of 46 patients were much improved or very much improved (CGI-I = 1 or 2) based on their aggressive symptoms, self-injurious behaviors or severely disruptive behaviors. Two out of 46 patients were slightly improved (CGI-I = 3). Five (11%) of 46 cases were not improved or worsened (CGI-I = 4 or greater). Although not quantified, there was little to no benefit treating other symptoms present, such as hyperactivity, repetitive behaviors, attention, and mood.

Only two patients (4.2%) needed to be discontinued due to side effects (both bronchial constriction). 30 patients on high dose propranolol had cardiology workup and other than some bradycardia and reduction in pulse (not clinically significant) there were no adverse effect on Holter monitor or echocardiogram.

1.5 Sample Size Justification

McNemar's test will be used to compare the percentage of participants achieving treatment response on propranolol as opposed to placebo. The preliminary pilot data (London et al., under review) showed an 85% response to propranolol. Assuming a 20% placebo response and a conservative estimate of a 75% propranolol response, we require 17 participants to detect a difference of (75-20) percent. To account for an anticipated drop-out rate of 15%, 24 participants will be recruited. Given the gender rate of 4:1 male to female prevalence of ASD, we expect more male participants (18 males: six females).

1.6 Study Variables

A. Independent Variables, Interventions, or Predictor Variables

Describe any treatments or interventions to be compared for their effects on participants.

Propranolol

We are using a beta blocker, propranolol, as an independent variable to investigate its effects on people with ASD who present with chronic challenging behaviors. Propranolol has been used worldwide for over 50 years (Black, Crowther, Shanks, Smith, & Dornhorst, 1964). It has been listed by the World Health Organization as one of the ten most important medications. Safety concerns are well known and

are quite manageable. Its primary indication is for heart problems (high blood pressure) but has also been used to:

- control heart rhythm in atrial fibrillation
- relieve angina (i.e., chest pain)
- prevent migraines
- reduce shaking or essential tremor
- help with medical conditions involving your thyroid and adrenal glands
- support heart function after a heart attack

There is evidence that at higher doses, propranolol inhibits rage and anger through effects on the central nervous system. This effect has been demonstrated in a variety of neuropsychiatric disorders including head trauma, schizophrenia, ASD, and other developmental disabilities. In addition, propranolol does not cause the significant weight gain or other side effects associated with the use of antipsychotic medications (viz. risperidone). Our preliminary experience has shown that 85% of a group of extremely aggressive adolescents and adults with ASD have "much improved" or" very much improved" when treated with propranolol.

Concomitant Medication and/or Behavior Intervention
Throughout the study the participants will **remain on their pre-existing medications** due to the severe nature of the problem behaviors and the ethical dilemma of the possibility of worsening symptoms by withdrawing medications for the sake of the study. The participants will be encouraged to continue all other treatments and educational (behavioral) programs they are on prior to the study throughout the study duration. However, any significant change in their other treatments such as a change in medication, or the institution of a new behavioral program which is significantly different from the program which they were on at the beginning of the study will necessitate the participant being dropped from the study.

B. Dependent Variables or Outcome Measures
List and describe all outcome measures that "depend on" your treatment, manipulation, or predictor variables.

Primary Dependent Measures

Name	Description	Time required
Clinical Global Impression--Improvement **(CGI-I)**	Is used to judge the overall clinical condition relative to baseline using the same scale as the CGI-S. The clinician will rate the improvement from baseline on a scale of 1=very much improved since the initiation of treatment; 2=much improved; 3=minimally improved; 4=no change from baseline (the initiation of treatment); 5=minimally worse; 6= much worse; 7=very much worse since the initiation of treatment.	5 mins

Aberrant Behavior Checklist-Community **(ABC-C)**	A global behavior checklist that measures drug and other treatment effects in people with developmental disabilities. It is made up of five subscales, including Irritability, Lethargy, Inappropriate Speech, Hyperactivity, and Stereotypy based on 58 items that describe various behavioral problems. The *Irritability* Subscale will serve as the primary dependent measure.	15 mins
Side Effects Questionnaire	A questionnaire for measuring patient-reported side effects of medication	5 mins

Secondary Dependent Measures (*goes along with Aim #3,* repeated at each study visit)

Name	Description	Time required
The Questions About Behavioral Function (QABF)	An indirect assessment of behavioral function for individuals with developmental disabilities. It contains 25 items. The QABF yields five behavioral function categories: Access to Attention, Escape from Demands, Physical, Access to Tangible, and Nonsocial (i.e., sensory or automatically-maintained). Each question is scored with frequency descriptors of Never, Rarely, Some, and Often.	5-10 mins
The IBR Modified Overt Aggression Scale (IBR MOAS)	A 107-item questionnaire that includes five types of aggression (verbal aggression towards self and others, physical aggression towards objects, self, and others) with four levels of severity for each type of aggression. Only the section assessing the 5 types of aggression will be used for repeat evaluations: *Verbal aggression toward others, Verbal aggression toward self, Physical aggression against other people, Physical aggression against objects, Physical aggression against self*. This scale provides a global assessments of aggression frequency. The IBR MOAS includes additional information on the antecedents and consequences of aggressive behaviors, clinical diagnoses, and etiologies (Cohen et al., 2010).	10 mins

1.7 Drugs/Devices/Biologics

Describe the regimen (drugs, doses and schedule by which the treatment will be given), and drug administration guidelines

A. Medication Dispense, Randomization, and Medication Dispense

At the first treatment visit, the participant will be randomly assigned to propranolol first or placebo first (Phase A or Phase B) based on a computer-generated randomization schedule prepared by the research pharmacist. The medication will then be supplied by the Rutgers Research Pharmacy. The pharmacists alone will supply active medicine and placebo with all other study personnel blinded.

The randomization will be balanced by using randomly permuted blocks. Based on this randomization code, the study drug will be packaged and labeled for each participant. Medication numbers will be preprinted on the study drug labels and assigned as participants qualify for the study and are assigned to

treatment.

Study drug labels have peel-off panels printed with corresponding medication numbers to be removed and attached to the participant's case report form (CRF) or drug accountability logs when the drug is dispensed. The core part of the label remains affixed to the study drug container and will have all identifying information except for the dose of the drug. The study drugs will be identical in appearance and will be packaged in identical containers. To maintain the blind, sealed envelopes containing the study drug identification (i.e., propranolol or placebo) will be provided to the investigator. These sealed envelopes will be kept together, in a limited access area that is accessible 24 hours per day. The same information will be kept in a shared restricted folder for the PI and Pediatric cardiologist to access in case of emergency.

The study drug and placebo will be supplied in a liquid form and will be matched for color and taste. The standard dosing will be 10 mg tid (3 times per day), 40 mg tid, 80 mg tid, 120 mg tid, 160 mg tid and 200 mg tid (PHASE A) or matching placebo (PHASE B). All patients will begin at dose one (10 mg tid or 30 mg per day)

Study DRUG PHASE A	**Strength**	**FREQUENCY**	**TOTAL DAILY**	**Placebo Phase B**	**FREQUENCY**
Dose 1 10 mg	20 mg/ml	½ ml tid	30mg	Dose 1	½ ml tid
Dose 2 40 mg	40 mg /ml	1 ml tid	120mg	Dose 2	1 ml tid
Dose 3 80mg	40 mg /ml	2ml tid	240mg	Dose 3	2ml tid
Dose 4 160mg	40 mg /ml	3 ml tid	480mg	Dose 4	3 ml tid
Dose 5 200mg	40 mg /ml	4 ml tid	600mg	Dose 5	4 ml tid

The Research Assistant will be responsible for ensuring delivery of study drug to the subject. The first dose will be given to the subject's family during the Baseline phase. The research doctor (psychiatrist) will be responsible for determining the study drug dose each week. The Research Pharmacy will prepare the study drug and the Research Assistant package the study drug for express delivery or courier/ or supply to family after study visit.

The dose changes will be stepwise and flexible to allow for subject tolerability. The dose will be titrated until adequate therapeutic response is obtained (as decided by the parents and psychiatrist) or up to a dose of 600 mg per day (note: propranolol is FDA-approved up to a dose of 640mg). If there is suboptimal response (based on the judgment of the psychiatrist and the parent or caregivers), the dose can be raised as frequently as once per week. The titration schedule however will be flexible and the dose can be held steady for an extended period primarily if it is deemed that additional observation is needed prior to increasing the dose. The downward titration schedule can be slower, depending on clinical factors (although this was not needed in our preliminary study--London et al., under review).

Scheduled dose increases could be delayed because mild adverse effects (i.e. some nausea, tiredness or difficulty adjusting to medication or parent preference) or because of marked improvement at a lower dose.
Dose reduction to manage side effects are allowed at any time.

In addition, we will monitor side effects Medication will be held for participants with HR < 90/50 and HR < 50 awake in asymptomatic subjects. Families will be instructed to ensure patient is adequately hydrated and to hold medication during fever and GI illness with vomiting or diarrhea.

B. **Drug/Device Accountability And Storage Methods**

The Research pharmacist at RWJ Medical School Pharmacy/Investigational Drug Service will properly store and dispense all investigational drugs (active and placebo) and maintain accurate dispensing and inventory records. Propranolol does not require a special temperature control. This includes keeping records of:

1. Receipt and inventory of investigational drugs
2. Storage of investigational drugs
3. Dispensing of investigational drugs and
4. Return or disposal of the investigational drugs.

The Research pharmacist at RWJ Medical School Pharmacy/Investigational Drug Service will be responsible for preparation, dispensing and disposal of the study drug. The Research Coordinator will be responsible for collection of all unused study medication from families and delivery of study medication to the research pharmacist for disposal.

The Principal Investigator and Research Coordinator will also ensure that the entire research team (co-investigators, research pharmacist, research assistants) and the participant's family understand the procedures necessary to maintain drug accountability and follow the study protocol.

C. Medication Compliance: Throughout the study, the investigator or study nurse will maintain a log of all study drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study. Study drug will be measured weekly. Compliance will be assessed by the amount used of the oral solution in the drug container.

If a participant fails to take his or her dose of study drug for 3 or more consecutive days during the double-blind treatment and open-label phase, the participant must be withdrawn from the study.

1.8 Primary Specimen Collection: N/A

1.9 Interviews, Focus Groups, or Surveys:

1.9A. We will not conduct interviews, focus groups, or surveys.

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1.9B. Study Instruments

Diagnostic and Functional Measures- used to confirm ASD diagnosis and characterize subjects social, adaptive and functional impairment by behavioral difficulties.		
Name	Variables of Interest & Study End-Points	Reliability & Validity
Autism Diagnostic Observation Schedule-2 (ADOS)	Documentation of ASD diagnosis	Lord et al. (1989)
Vineland Adaptive Behavior Scale (VABS-III)	Documentation of personal and social functioning around four Behavioral Domains: Communication, Daily Living Skills, Socialization, and Motor Skills	Perry & Factor (1989)
Leiter-3	Nonverbal test of intelligence and cognitive abilities	Roid et al. (2013)
Social Communication Questionnaire (SCQ)	Evaluate the symptoms of ASD during anytime during Life and at the Current time for adult participants who lack adequate diagnostic documentation for ASD and who are not suited for the ADOS-2.	Brooks & Benson (2013
Clinical Global Impression-Severity (CGI-S)	Used to judge the severity of behavioral problems prior to entry into the study	Guy (1976)

Primary Dependent Measures		
Name	Description	Reliability & Validity
Clinical Global Impression--Improvement (CGI-I)	Used to judge the overall clinical condition relative to baseline using the same scale as the CGI-S.	Guy (1976)
Aberrant Behavior Checklist-Community (ABC-C)	Checklist to measures drug and other treatment effects in people with developmental disabilities. The Irritability Subscale will serve as the primary dependent measure. The ABC-C was validated on 509 people with developmental disabilities.	Aman et al. (1985),
Side Effects Questionnaire	A questionnaire for measuring patient-reported side effects of medication	N/A

Secondary Dependent Measures		
Name	Description	Reliability & Validity
The Questions About Behavioral Function (QABF)	An indirect assessment of behavior function for individuals with developmental disabilities.	Paclawskyj et al. (2001)
The IBR Modified Overt Aggression Scale (IBR MOAS)	This scale provides a global assessments of aggression frequency.	Cohen et al. (2010)

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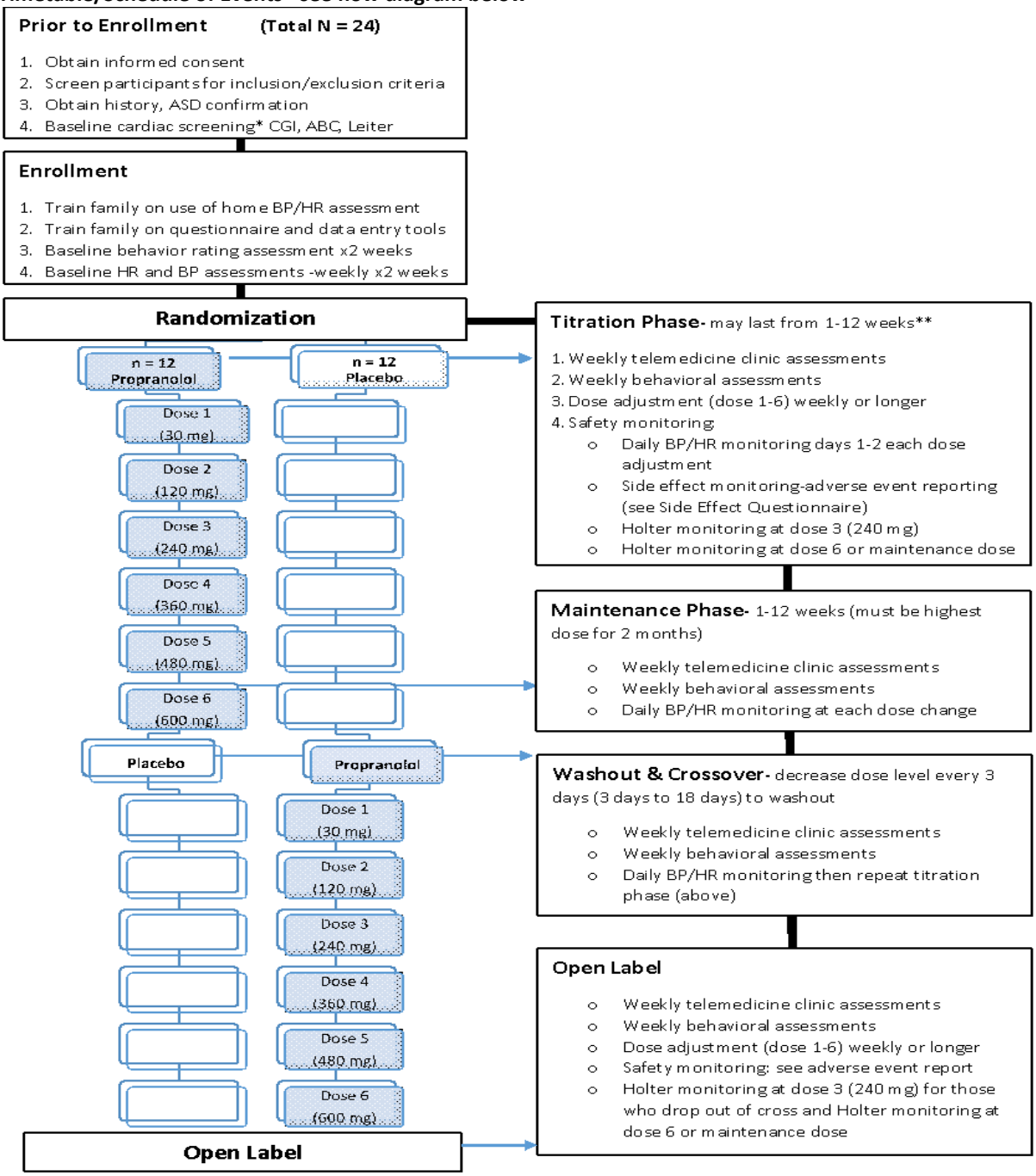
1.10 Timetable/Schedule of Events –see flow diagram below



2.0 Project Management

2.1 Research Staff and Qualifications

Our team is *not* new to autism spectrum disorder (ASD) research. Dr. Zimmerman-Bier (PI) and Dr. Eric London (Co-PI) have collaborated on autism spectrum disorder related research projects for eight years. Currently, they have three funded NJACE Pilot projects that are housed within Child Health Institute /Department of Pediatrics- RWJMS/Rutgers (CAUT15 APL045, CAUT15 APL046 and CAUT16APL025).

Dr. Zimmerman-Bier, M.D. (Co-Principal Investigator) is a board certified Developmental Pediatrician with expertise in the assessment / treatment of adolescents and young adults with autism spectrum disorder. Dr. Zimmerman Bier is PI on three currently funded NJACE Pilot grants. She has extensive experience in leading multidisciplinary assessment teams and clinical trials in autism spectrum disorder. She is research certified in the ADOS-2 and ADI-R.

Eric London, M.D. (Co-Principal Investigator) is a board-certified psychiatrist and Director of the Autism Treatment Research Laboratory at the New York State Institute for Basic Research (IBR; non-Rutgers institution). He is the founder of National Alliance for Autism Research (NAAR) and a Scientific Reviewer for NIH CPEA/STAART grants. He has 34 years of clinical experience treating comorbid psychiatric disorders in ASD. He has extensive expertise in the use of propranolol in highly aggressive adults with autism spectrum disorder. The preliminary data for this proposal, is based on the clinical data provided by Dr. London. Dr. London will be serving as the study doctor (psychiatrist) and will be responsible for study drug titration. He will meet with the participants and families weekly by telemedicine.

Marc Sturgill, Ph.D. (Co-Investigator) is an Associate Director of the Pediatric Clinical Research Center and Chair of the Department of Pharmacy. He has published more than 30 peer review journal articles and/or abstracts describing the results of clinical trials in adults and children, including both compartmental and noncompartmental pharmacokinetic modeling and statistical analysis.

Joseph Gaffney, M.D. (Co-Investigator) is the Chief of Pediatric Cardiology at RWJMS/Rutgers and has extensive experience in the cardiac assessment of adolescents and young adults. He leads a team of physicians, nurses, technicians and allied health professionals involved in the care of individuals with complex medical needs, including those with comorbid behavioral disorders.

J. Helen Yoo, Ph.D. (Co-Investigator) is a licensed psychologist and a licensed behavior analyst. She served as a research assistant on several NICHD-funded psychopharmacology studies in people with developmental disabilities. At the New York State Institute for Basic Research (IBR), she served as the PI on a 5-year program that provided school-based functional behavior assessment and function-based intervention to children and adolescents who engage in severe and chronic challenging behaviors. She is research-reliable on the ADOS-2 and the ADI-R.

Database Developer (TBD) will work directly with the IT department at RWJ and research team on necessary files for questionnaires and clinical data, data integrity, study databases, and will also train staff on production and tracking of analytic data files.

Research Coordinator (RC) will prepare study related information materials and answer questions about the study. The RC will assist with patient recruitment and enrollment, provide family training on the use of the HR /BP monitor and the telehealth. The coordinator will monitor retention and scheduling of research testing. The RC will work with the PI's on reports for the NJ Governor Council and attend meetings with the Coordinating Center. The RC will ensure all project members are trained on the research protocol and that IRB protocols are followed.

2.2 Resources Available

Robert Wood Johnson Medical School is one of the professional schools of Rutgers, The State University of New Jersey. The Child Health Institute, The Pediatric and Adult Clinical Research Centers, The Pediatric Cardiology Program and the Pharmacy/Investigational Drug Service are all part of RWJ Medical School/Department of Pediatrics.

The Department of Pediatrics at RWJ Medical School conducts a number of investigator-initiated and pharmaceutical industry-sponsored Phase I-V clinical research efforts throughout the campus at UMDNJ-Robert Wood Johnson Medical School. The faculty and staff are trained and experienced in conducting clinical trials in children, adolescents and young adults. RWJ Medical School has a Clinical Research Center that is available to facilitate clinical research throughout the entire campus. The Department of Pediatrics has many ongoing investigator-initiated and pharmaceutical industry-sponsored Phase I-V clinical research. The Research Pharmacy will provide logistical and regulatory services needed for this clinical research study.

Pharmacy: Investigational Drug Service (IDS) is a cooperative service with the Department of Pharmacy of the Robert Wood Johnson University Hospital. The IDS is responsible for the storage, security, preparation and proper labeling, randomization and dispensing of study medications in clinical trials. The service is involved in creation of pharmacy portions of investigator-initiated protocols and in the acquisition of drug product for studies within the medical school community. The Research Pharmacy provides expert consultation during the development of clinical trials. The staff focuses on the development of exclusion criteria for concomitant medications that may interact with the protocol agent, exclusion criteria and dose modifications.

Cardiology: The Children's Heart Program of New Jersey at Robert Wood Johnson Medical School (RWJMS) is a center of excellence, providing comprehensive services to infants, children, adolescents and young adults. The Department is staffed by four full time pediatric cardiologists that provide 24 hour/7 days per week coverage, as well as nurses, technicians, and office staff. The pediatric cardiology

outpatient clinic located in the Clinical Academic Building of RWJMS. Clinics are held five days per week. The outpatient office provides comprehensive cardiac evaluations including echocardiography, EKGs, 24-hour Holter monitoring, transtelephonic cardiac rhythm monitoring, and cardiodynamic exercise testing.

Psychological/Behavioral Consultation: At the termination of the research participation (including early withdrawal), a licensed clinical psychologist (J. Helen Yoo, co-investigator) will meet with each participant and his/her family to make appropriate behavior-analytic recommendations regarding the behavioral management of severe challenging behaviors. If necessary, referrals to behavioral providers will be made, as well as referrals for support groups.

Data Systems and Data Support Staff: The RWJ Information Systems, services provided 24-hours a day, 7-days a week, 365 days a year. The RWJ has collaborated with The Department of Pediatrics to develop a comprehensive HIPPA compliant telemedicine platform. The telemedicine platform utilizes two way videoconferencing.

Research Staff Training: In order to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions, we will hold one introductory training overview with all staff, followed by a mock run-through of a fictitious participant (e.g., graduate student) through all study procedures, then another training to clarify and finalize the study procedures. A detailed study procedure manual, including emergency contact information will be available on a shared research drive.

2.3 Research Sites

Research activities will occur at Children's Health Institute and the Pediatric Cardiology Center at Robert Wood Johnson Medical School. The research coordinator will also be available to train the caregivers (on site or at the subjects' home) on how to administer the study medication, enter behavioral data (i.e., questionnaires), and take heart rate and blood pressure data. Following the initial study enrollment, HIPAA-compliant telemedicine will be used on a weekly basis in order to eliminate the travel burden for the participant and their caregivers.

3.0 Multi-Site Research Communication & Coordination

3.1 Outside Research N/A

4.0 Research Data Source/s

4.1 Primary Data-Subjects and Specimens

4.2 Subject Selection and Enrollment Considerations

A. Recruitment Details

General: Recruitment activities take place under the Office of Research and the guidance provided by the IRB at Rutgers/RWJ Medical School. The study will take place under the supervision of the Pediatrics Department and IRB at RWJ Medical School. The Subject Pool includes adolescents and adults with a diagnosis of ASD and significant symptoms of aggression or self-injury.

B. Source of Subjects

Recruitment Procedures: Information about the study will be provided to physicians, special educators, behavior analysts, and voluntary agency staff and family advocacy groups through flyers, advertisements and on the RWJ research websites and social media (e.g., Facebook). The study will be registered at Clinicaltrials.gov.

C. Method to Identify Potential Subjects

A separate phone line will be created for families and local practitioners to get information about the study. Children's Specialized Hospital, Robert Wood Johnson Psychiatry Department and the RWJ. Neurology Department provide extensive medical and behavioral services for many adolescents and adults with ASD. We will also reach out to the local special education schools, voluntary agencies, and developmental disabilities service providers (psychiatrists, neurologists, developmental pediatricians, behavior analysts) with the study advertisement. We do not anticipate difficulty with recruitment.

Retention: Each participant will be followed through the pre-enrollment phase, enrollment, randomization, titration phase, maintenance and cross over phase and open label portion of the study through standardized study visits and safety monitoring. We will be enrolling 24 participants to allow for potential drop out. Procedures to optimize retention and decrease study burden:

1) The initial cardiac function visit will require families to visit the hospital. Financial barriers include costs of traveling and parking for the clinic appointment, and missed work. Our study will provide stipends to defray the cost of transportation/parking.
2) We are using a telehealth platform (Skype-like) for the clinical follow up. Families will receive tablets through the study, or can use their cell phone or computers, for clinical follow up visits with clinicians. We are utilizing home Holter monitoring with equipment that has been used in other research studies. Families will use prepaid mailers to return the Holter monitors at the end of their participation in order to minimize the frequency of travel for clinic visits.
3) We are using web based platforms (RedCap) to enable families to complete questionnaires which can be completed at home.
4) The participants enrolled in the placebo arm of the study will most likely have a delay in treatment with the study agent, and could be more likely to drop out. However, all families will

be given the opportunity to "un-blind "from the treatment arm and then enroll in the open label portion of the study. This will allow us to continue to monitor the safety and efficacy of the study medication while minimizing the study burden.

5) We will keep frequent contact (weekly) with study participants to address any concerns related to study burden.

D. Subject Screening – initial telephone screening (see attachment for telephone screening) will occur by the Research Coordinator using the following inclusion and exclusion criteria.

Inclusion Criteria

1. Males and females between the ages of 12-30 years and NJ residents.
2. Diagnosis of ASD conducted by a clinician with confirmation such as ADOS-2 or SCQ.
3. At least one of the following challenging behaviors:
    a. Self-injurious behaviors (i.e. hitting one's self, head banging or banging of other body parts causing some degree of tissue damage);
    b. Physical aggression towards others (i.e. hitting, kicking, pushing, spitting or throwing objects at others);
    c. Disruptive behaviors including property destruction during anger episodes, excessive screaming which interferes with functioning; and
    d. The challenging behaviors are generally (but not necessarily exclusively) associated with a congruent affect (i.e. anger or rage when aggressing) as determined by the study psychiatrist.
4. Pharmacologic treatment with at least two psychotropic medications including one antipsychotic medication has yielded inadequate outcome (partial improvement on one or more medications is acceptable for the study).
5. *Clinical Global Impression* Severity scale (CGI-S) score of 6 or 7 (severely impaired or most severely impaired).
6. *Aberrant Behavior Checklist--Community* (ABC-C) Irritability scale score at or above 18
7. Medical and cardiac clearance.

Exclusion Criteria

1. Asthma or any history of asthma or any disorder involving bronchoconstriction
2. Cardiac Diseases in which the use of propranolol at high doses would be contraindicated
3. Uncontrolled Seizure disorder. (seizure free for > 1 year and no changes in seizure medication in the previous six months)
4. Diabetes or a history of ketoacidosis
5. Any other medical disorder or medication which would contraindicate the use of propranolol
6. History or allergy or adverse reaction to propranolol

7. Pregnancy
8. Medication exclusions include clonidine/guanfacine / methylphenidate or dexamphetamine l (or similar ADHD medications/ digoxin or other medications affecting blood pressure

E. Recruitment Materials

Recruitment materials are attached: flyers, letter to the doctors, letter to the educators,

F. Lead Site Recruitment Methods: N/A

4.3 Subject Randomization

Simple randomization will be utilized to allow for complete randomness of the assignment of a subject to a group. With the two treatment groups (placebo first versus treatment first), a computerized random number generator will be used for simple randomization of participants.

It is possible that simple randomization method may lead to an unequal number of participants among the two groups. Therefore, the research pharmacist will have the option to balance the group assignment for the last 3 participants.

4.4 Secondary Subjects

Participants' legal guardians will become secondary participants as a result of the information provided on behalf of the primary participants. We will take appropriate precautions for data security in order to minimize a breach of confidentiality or an invasion of privacy to both primary and secondary participants from information disclosure. During the study visits, we may observe embarrassing behaviors or inadvertently discover sensitive information about secondary participants. If the risks are legal in nature, such as observations of unsafe conditions or unlawful behaviors that may need to be reported to law enforcement agencies, then proper procedure will be followed. In all other cases, the secondary participants' Consent will be collected during the very first contact and continue throughout the study.

4.5 Number of Subjects

A. Total Number of Subjects: 24

B. Total Number of Subjects If Multicenter Study: N/A

B. **Required Number of Subjects to Complete Research**: 17

D. Feasibility of Recruiting

Participants will be recruited from the local New Jersey community and surrounding areas, including schools, voluntary agencies, and parent support groups. We do not anticipate challenges related to recruitment.

4.6 Consent Procedures

A. Consent

Documenting Consent -

- Our study involves adolescents and adults with severe behavioral difficulties and ASD who have failed conventional treatments with at least 2 antipsychotics as well as behavioral therapy. Our participants will not have the mental capacity to consent. We will require a parent or legal guardian (for participants over age 18). Parent or legally acceptable representative's consent will be obtained in writing. The participants and his/her legally acceptable representative are informed of all facets of the study. This includes information that the study will employ ***double-blind, placebo-controlled study design***, and that the participant will receive both the active drug and placebo at some point in the study.

-

- **Waiver of <u>Documentation</u> of Consent:** N/A This research does not use deception/concealment.

B. Consent Process

- **Location of Consent Process**
  Consent will be obtained at the Pediatric Clinical Research Center (PCRC) /Child Health Institute (CHI) located on the first floor 89 French Street New Brunswick.

- **Ongoing Consent**

  - Before entry into the study, the investigator or an authorized member of the research staff will explain to the potential participant and his/her parents, or his/her legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, as well as any discomfort participation may entail. Our study population will not be competent to give informed consent. In that case we will proceed with the responsible party.
  - They will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive from Rutgers for the treatment of his/her condition. Participants will again be told that alternative treatments are available if they choose not to take part and that such refusal will not prejudice future treatment.
  - The participant and his/her parent, or legally acceptable representative will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, assent and consent will be appropriately recorded by means of the participant's assent and the signed and dated consent of the participant's parent or legally acceptable representative. After having obtained the consent, a copy of the informed consent form will be given to the participant and his/her parents or legally acceptable representative.

- **Individual Roles for Researchers Involved in Consent-**

  All study personnel will receive training prior to start date of the study. There will be a kick-off meeting with the PI and COPIs as well as research assistants. The PI and research assistants will be organizing consent meetings, providing the consent forms and answering participant questions throughout the consent process.

  - **Consent Discussion Duration**

    The initial consent meeting and discussion will take at least 45-minutes. Thereafter, the consent (i.e., continuation with study participation) and the upcoming study procedures will be discussed at each study visit and as necessary.

  - **Coercion or Undue Influence**

    Participants and their parents or legally acceptable representatives will be informed that their participation is entirely voluntary and that they may withdraw consent/assent at any time.

  - **Subject Understanding**

    Minors or participants who are unable to comprehend the information provided can only be enrolled after obtaining consent of his/her parent or legally acceptable representative. However, assent will be obtained from participants capable of understanding the nature of the study (typically participants with mental age of approximately 7 years of age and older).

4.7 Special Consent/Populations

This research involves minors and adults with cognitive and developmental disabilities.

A. Minors-Subjects Who Are Not Yet Adults

- **Criteria for Consent of Minors – Participants less than 18 years of age will be considered minors.** Consent of minors will not be acceptable due to a diagnosis of intellectual disabilities being an inclusion criterion. Parent or legally acceptable representative's consent will be required.
- **Wards of the State N/A**
- **Parental Permission**

Parent or legally acceptable representative's consent will be required. (A legally acceptable representative is an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to his/her participation in the procedures involved in the research.)
Also, both parents must give their permission unless one parent is deceased, unknown, incompetent, not reasonably available, or when only one parent has sole legal responsibility for the care and custody of the research participant.

- **Non-Parental Permission**
  Only parents and legally acceptable representative's consent (a court-appointed legal guardian) will be able to provide consent for participation in this research study. For minors who have a legal guardian (non-parental), we will review the guardianship authorization and complete the Surrogate Certification Form.
- **Assent Process**

  Assent will be obtained from all participants capable of understanding the nature of the study (typically, participants with mental age of 7 years of age and older). Every effort must be made to maximize the factors that would promote the ability of the participant to assent.

  - **Documentation of Assent**
    Assent will be documented on the consent form by the individual obtaining informed consent.
    .
  - **Non-English Speaking Subjects N/A**
    The consenting parent or legally acceptable representative must speak English in order to complete all study procedures.

B. Adults Unable to Consent / Cognitively Impaired Adults (*for interventional studies*)

- **NJ Law-Assessment of Regaining the Capacity to Consent**

All adult study participants, due to the study inclusion criterion of ASD and cognitive and developmental disabilities and symptoms of severe aggressive behaviors, will be unable to consent. By the age of 18, parents/ other caregiver will have completed the process of obtaining guardianship for the adult participant. The guardianship process is a legal proceeding and requires two physicians to certify that the subject is unable to make health care decisions. These physicians are not associated with the research study. Because ASD and developmental disabilities are a pervasive, life-long condition, if the participant does not have the capacity to consent during the study enrollment, it is highly improbable that the participants will gain the capacity to consent at a later time.
We will review the guardianship authorization and complete the Surrogate Certification Form. The parent guardian or legally acceptable representative will provide surrogate consent.

- **Capacity To Consent**

All adult study participants, due to the study inclusion criterion of ASD and cognitive and developmental disabilities and symptoms of severe aggressive behaviors, will be not have capacity to consent.

- **Wards of the State**: N/A

- **NJ Law-Selecting A Witness**

For studies at RWJ, an independent advocate who is familiar with informed consent process who is unrelated to this research project will be the designated witness for surrogate consent. We will be utilizing the Research staff at the Institute for Child Development (ICD) who are not involved in our study. The research staff at ICD are trained on informed consent procedures. The written consent form will be signed and dated by the ICD research staff, who will serve as a witness.

- **Removing a Subject**

In the event the participant or his/her legally acceptable representative expresses dissent or withdraws consent, the study blind will be broken.

- If the participant was taking placebo, it will be immediately stopped.
- If the participant was taking the active medication at the time of termination, he/she will still need to safely undergo a titration down to no medication. This may require several additional study visits or telemedicine calls.

A follow-up for 2-weeks beyond the last day of active drug administration will also be required. However, the participant and his/her legally acceptable representative may also elect to seek follow-up from their primary care physician instead. The study psychiatrist will communicate directly with the primary care physician in such case, with the written authorization from the participant and his/her legally acceptable representative. The study psychiatrist will also be available via 24-hour emergency phone number.

4.8 Economic Burden and/or Compensation for Subjects

A. Expenses

There will be no cost to the participant and his/her legally acceptable representative for participating in this study. For study visits that require the participant and/or his/her legally acceptable representatives to be present at RWJMS, parking will be paid by the study at the completion of the entire project.

B. Compensation/Incentives

All research-related materials and procedures will be provided by the study. Parking at RWJMS will be paid for. Each participant will also receive [$50.00] to help cover other expenses (e.g., travel) for attending study visits. The payment will be made at the end of the entire research study (note: not at the completion of each participant's involvement in the study).

C. Compensation Documentation

After completion of the study, participants will receive a gift card. The participant's parent or legal guardian will be asked to sign the Gift Card Release Form to confirm receipt of the gift card. The Gift Card Release form which will be dated and signed by research staff. These forms will be kept in the study binders.

4.9 Risks to Subjects

A. Description of Subject Risk

Risks from Propranolol: some participants may experience slower heart rate, diarrhea, dry eyes, hair loss, nausea, weakness or tiredness.

Discomforts: The participant may experience physical discomfort while undergoing study procedures such as wearing the Holter monitor and during EKG.

Inconvenience: This study requires many visits that takes time away from the participant's regular daily activities. Moreover, participant's ongoing interventions (e.g., behavior therapy) are to remain constant without significant changes.

B. Procedures for Risks to Embryo, Fetus, and/or Pregnant Subjects: N/A

C. Risks to Non-Subjects
Parents or legally acceptable representatives may feel uncomfortable answering questions about the participant's challenging behaviors, especially if those behaviors have led to risk/harm to the participant and/or others in the past.

D. Assessment of Social Behavior Considerations

a)Reasonably Foreseeable Risks

Propranolol: Participants may experience worsening of challenging behaviors or they may experience side effects with the use of propranolol.
Titration and Washout: The result of increasing or stopping the study medicine could cause the participant's challenging behaviors to worsen.

b) Risk Of Imposing An Intervention On Subject With Existing Condition

The risk of imposing a medication and placebo on people with ASD and severe challenging behaviors is assuming that the individual wants to participate and potentially ameliorate these symptoms. Because the majority of participants who meet the inclusion and exclusion criteria do not have sufficient ability to communicate and make medical decisions the ability and opportunity to communicate choices and exercise control over such decisions are assumed by the parent or his/her legally acceptable representative.

c) Other Foreseeable Risks-participant may feel mild discomfort during Holter monitoring.

d) Observation And Sensitive Information

Sensitive information may be disclosed during study visits in-person and during telemedicine conferences. Unless the information relates to direct harm or neglect of those involved, all information will be held confidential.

E. Minimizing Risks- Safety Monitoring

This is a vulnerable population, and as such, our study requires that the study participants receive the most careful protection at every stage of the evaluation and treatment.
The major side effect which we will be vigilant about are the cardiac side effects. We will continuously monitor pulse and blood pressure and any adverse events carefully throughout the study. The participants' parents will have access to telemetric monitoring devices to transmit data at any time.
Below is a summary of the safety measures for this study:

1. An independent Data and Safety Monitoring Board (DSMB) will be established to ensure the safety of research participants and the integrity of the study data. We have identified experts in the fields of neurology/ASD/cardiology and research statistics who have agreed to serve on the DMSB. They are independent of this study and do not have any conflict of interest. The DSMB will meet prior to the enrollment of the first participant to review the research protocol, informed consent, and plans for safety and data monitoring of the study. Thereafter, the DSMB will meet periodically to monitor progress, efficacy, safety, and other confidential data from this study. The PI will provide a written report to the Board prior to each meeting. Topics to be discussed during the meetings include, but are not limited to, recruitment, protocol compliance, efficacy, and safety. All DSMB safety reports recommendations will be sent to the PI, including instructions on forwarding recommendations to the Rutgers IRB, the NJ Governor's Council, and regulatory agencies.
2. The dose will be stepwise and flexible to allow for subject tolerability. The dose will be titrated until adequate therapeutic response is obtained (as decided by the parents and psychiatrist) or up to a dose of 600 mg per day (note: propranolol is FDA-approved up to a dose of 640mg). If

there is suboptimal response (based on the judgment of the psychiatrist and the parent or caregivers), the dose can be raised as frequently as once per week. The titration schedule however will be flexible and the dose can be held steady for an extended period primarily if it is deemed that additional observation is needed prior to increasing the dose. The downward titration schedule can be slower, depending on clinical factors (although this was not needed in our preliminary study--London et al., under review).

3. Scheduled dose increases could be delayed because mild adverse effects (i.e. some nausea, tiredness or difficulty adjusting to medication or parent preference) or because of marked improvement at a lower dose.
4. Dose reduction to manage side effects are allowed at any time.
5. We have included a comprehensive cardiac clearance before patients are randomized to treatment arms. (See section **1.3 Research Design and Methods**) to identify subjects with any undiagnosed cardiac problems or increased likelihood of adverse reactions to the study drug.
6. A 24-hour Holter monitor exam will be completed at dose #3 (240 mg) and at maintenance dose to ensure no significant bradycardia or other cardiac issues ensue. Holter monitoring at high doses of propranolol (240 mg or more per day) will evaluate heart rate during sleep and look for arrhythmias. HR less than 30 during sleep or any arrhythmia will prompt discontinuation of medication.
7. In addition, we will monitor side effects (see side effect questionnaire screening for the most frequent side effects of propranolol), require blood pressure and heart rate to be completed during the first three days of each dose adjustment. Medication will be held for participants with HR < 90/50 and HR < 50 awake in asymptomatic subjects. A repeat blood pressure will be obtained prior to the next dose to ensure BP> 90/50 and HR > 50. The dose will be reduced if more than 2 doses of the drug are held.
8. There is a 24-hour call center for Pediatric Cardiology and parents can reach the study doctor (psychiatrist /PI) in case of concern.
9. Families will be instructed to ensure patient is adequately hydrated and to hold medication during fever and GI illness with vomiting or diarrhea. Prolonged illness necessitating holding more than 3 days of study drug will prompt breaking of the blind. Subjects will be offered the option of entering the open label portion of the study.
10. Adverse events will be reported by the participant and/or by the subject's parent, primary caregiver, or legally acceptable representative for the duration of the study, and serious adverse events will be recorded throughout the study and will be followed up until resolution. In addition, adverse events for the 30-days following completion of the study will be reported and followed by the investigator for 1 week or until resolution, whichever occurs first.

F. Certificate of Confidentiality

Certificate of Confidentiality will not be obtained.

G. Potential Benefits to Subjects

Our preliminary results have shown a significant decrease in aggression, self-injury, and/or disruptive behaviors in adults with ASD.

H. Provisions to Protect the Privacy Interests of Subjects

In order to protect the privacy interests of the participant, parent or legally acceptable representative will be present at all meetings with the research team. To minimize potential risks associated with privacy, each participant will be assigned and identified by a number. The key linking the participants' identifying data (e.g., name, DOB) and the participant number will be kept separately by the PI in a secure location. Data will be recorded, whenever possible, in a manner that does not allow participants to be identified, either directly or through identifiers linked to them.

I. Research Team Access To Subject Data

Only the authorized research staff will have access to study information and data. The data will be stored in a locked cabinet within a locked office in the PI office (1201) in the Children's Health Institute. Electronic data will be stored securely in password-protected computer with access limited to the study staff. The data will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal health information against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration will be put in place. Study personnel whose responsibilities require access to personal health information will keep the identity of study participants confidential.

4.10 Secondary Data – Records/Chart Reviews/Databases/Tissue Banks/etc.
Any records provided from the family such subjects previous diagnostic evaluations, school IEP or school testing will be stored in the subjects file after all identifiers are removed and replaced by the research assigned ID number.

4.11 Chart/Record Review Selection -
Records reviewed will be provided by subject family to assist with subject enrollment.

4.12 Secondary Specimen Collection N/A

5.0 Special Considerations

5.1 Health Insurance Portability and Accountability Act (HIPAA) N/A

5.2 Family Educational Rights and Privacy Act (FERPA)

For participants who are school-age, we will obtain educational records from the parents or legally acceptable representative, when available. These records include individual educational plans, psychological evaluations, functional behavior assessment and behavior intervention plans.

5.3 NJ Access to Medical Research Act

All study participants, due to the study inclusion criterion of ASD and cognitive and developmental disabilities and symptoms of severe aggressive behaviors, will be unable to consent. Parent or legally acceptable representative's consent will be required.

5.4 Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)

This study includes minors and adults with cognitive impairment and developmental disabilities.

1. This research involves greater than Minimal Risk to participants.
2. This research presents the prospect of direct benefit to the individual participant.
3. The risk is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual participant.
4. The risk to participant is presented by a monitoring procedure that is likely to contribute to the participant's well-being.
5. The risk is justified by the anticipated benefit to the participants.
6. The relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches.
7. Participants will be withdrawn if they appear to be unduly distressed.
8. There is a proposed plan for the assessment of the capacity to consent.
9. The participant will be informed about the research to the extent compatible with his/her understanding.

6.0 Research Data Protection and Reporting

6.1 Data Management and Confidentiality

A. Data Analysis Plan

1) Aim #1- To demonstrate the feasibility of treating and evaluating severely behaviorally impaired participants with aggression, self-injury, and disruptive behaviors who are diagnosed with ASD, using high dose propranolol to obtain blinded randomized data from which to justify a major placebo controlled clinical trial.
    a) Hypothesis #1- High dose propranolol will show evidence of being effective in treating the symptoms of aggression, self-injurious behaviors and disruptive behaviors, defined as greater than a 25% reduction in the ABC-C Irritability

subscale and a rating of much improved or very much improved on the CGI-I scale.

Aim #1 will be considered nominal in nature. Since this data is paired, McNemar's test will be used to compare the percentage of patients achieving treatment response on propranolol as opposed to placebo. The preliminary pilot data showed an 83 percent response to propranolol.

Assuming a 20% placebo response and a conservative estimate of a 75% propranolol response, we will need to recruit 17 subjects to detect a difference of (75-20) percent. To account for an anticipated drop-out rate of 15 percent, 24 subjects will be recruited.

Outcome measures- Treatment response will be defined as a composite endpoint including [a] greater than a 25% reduction in the ABC-C Irritability subscale score, and [b] a score of 2 or lower (much improved) on the CGI-Global Improvement scale.

2) Aim #2- To document the cardiac safety of various dosing levels of propranolol through follow up blood pressure/heart rate (BP/HR) and repeated Holter monitoring.
    a) Hypothesis #2- On high doses of propranolol (daily dose of 240 mg or more), there will be a drop in heart rate and blood pressure; however, this will not be clinically significant (HR < 90/50 and HR < 50 awake and HR< 30 while sleeping and no significant dizziness or fainting or near fainting that would necessitate discontinuation of treatment. Holter monitoring those at high doses will not show any arrhythmias.
    b) Hypothesis #2a- At higher doses, propranolol may cause a non-clinically significant decrease in heart rate and/or blood pressure.
    c) Hypothesis #2b- Holter monitoring of individuals at a propranolol dose of 240 mg/day or on maintenance dosing will not show any arrhythmias.

Aim #2 will be considered numeric. A repeated-measures analysis of variance (ANOVA) will be used to compare BP, HR, and HR variability at baseline, on maintenance dosing, and if applicable at a propranolol dose of 240 mg/day. A Friedman two-way ANOVA will be used for data that is not normally distributed. A Friedman two-way ANOVA will also be used to compare BP, HR, and HR variability at baseline, on maintenance dosing, and if applicable at a propranolol dose of 240 mg/day between propranolol and placebo patient cohorts.

3) Aim #3- To evaluate and analyze the sensitivity and specificity of the secondary dependent measures of challenging behaviors in order to develop novel and innovative data collection methods of studying this population. These novel methods will be used to develop more rigorous and adequately powered studies in the future.

Aim #3 will be considered ordinal. A Friedman two-way ANOVA will be used to compare ABC-C, QABF, CGI, and IBR MOAS questionnaire results at baseline to those obtained at the end of each propranolol dosage titration.

B. Provide a power analysis

All analyses will be intent-to-treat, including all randomized participants who receive at least one dose of double-blind study drug, propranolol. A P value less than 0.05 will be considered statistically significant.

C. *Describe the steps that will be taken secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.*

All study personnel will receive training prior to start date of the study. There will be a kick-off meeting with the PI and Co PIs as well as research assistants. All study-related staff will receive data safety and confidentiality training. Research Staff will ensure the identity of the participants and data collected remains confidential. The following safeguards will be implemented to maintain human subject confidentiality:

- Each participant will be given a unique study identification number. These identifiers will be transcribed into a logbook with corresponding subject name. The logbook will be kept in a locked cabinet in the PI's office.
- Only the personal study ID will be used on data collection sheets where clinical data will be transcribed.
- Participants' identifiable information (such as name, DOB, MR number) will be removed from collected reports and replaced with the participant unique study I.D. These reports will be stored in participant binders and kept in a secure locked cabinet in the PI office.
- Information from the data collection sheets (using only subject unique ID) will be entered into the RedCap database which will be secured with password protection. Data collection sheets stored in the subject's binders.
- Subject data will be entered into a password-protected database RedCap Database.
- Subject's parent and legal guardian will complete behavioral data (i.e., questionnaires) online through RedCap. Each participant will be emailed a link which opens to a behavioral form with subject ID and no identifiers. Once the form is completed by the family member, it is automatically uploaded to the RedCap database. Subject parent and legal guardian will not be able to view the database or other subject files.
- Any publication will not include any identification of the study participants
- The link between the subject unique I.D .and subject names will be destroyed after the completion of data collection and data analysis.

- The study data will be kept in a RedCap database for a minimum of 6 years after study closure or publication of the data.
- Confidential information obtained through written consent will be held exclusively by the study's investigators and will in no way influence the access to and quality of medical care provided.

D. Describe any procedures that will be used for quality control of collected data.

The PIs and the study staff will review all data on an ongoing basis for data completeness and accuracy. Data verification will be performed by someone other than the individual originally collecting the data.

E. *Describe how data be handled study-wide:*

- The study data will be kept in a password protected database for a minimum of 6 years after study closure or publication of the data.
- Access to the computerized data will be strictly limited to study investigators approved by the Institutional Review Board, except as required by law.
- The study research assistants will be inputting the data into the secure RedCap database. Our research team will receive secure passwords to allow for statistical analysis and team discussions. REDCap provides automated export procedures for seamless data downloads to Excel, PDF, and common statistical packages (SPSS, SAS, Stata, R).

6.2 Data Security

We will consult with the Rutgers Office of Information Technology to safety store all electronic data. Study personnel whose responsibilities require access to personal health information will keep the identity of the participants and data related to the study confidential. The data will be stored in a locked cabinet within a locked office. The information on the data collection sheet will be entered into a password-protected database RedCap Database with access limited to the study staff. The data will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. The REDCap application is a secure web application for building and managing online databases. REDCap can be installed for compliance with such standards as HIPAA, 21 CFR Part 11, FISMA and international standards. Access to the computerized data will be strictly limited to study investigators approved by the Institutional Review Board, except as required by law.

For questionnaires and HR/BP data that are collected and transmitted through the internet, the participant and his/her parent or legally acceptable representative will have the participant's assigned code, rather than name, when submitting the data. There are no foreseeable risks to participation except for the remote possibility that the responder's email or IP address would be inadvertently disclosed.

6.3 Data and Safety Monitoring

A. Periodic Data Evaluation

The PIs and the study staff will review all data on an ongoing basis for data completeness and accuracy as well as protocol compliance. Data verification will be performed by someone other than the individual originally collecting the data.

B. Type of Data Evaluated

Adverse Events will be labeled according to severity, which is based on their impact on the participant. An AE will be termed "mild" if it does not have a major impact on the participant, "moderate" if it causes the participant some minor inconvenience, and "severe" if it causes a substantial disruption to the participant's well-being.

C. Collection of Safety Information

Safety information will be collected using a side effects questionnaire and by the study psychiatrist during the regularly scheduled study appointments.

D. Frequency Of Data Collection

Data are collected during screening, baseline, and then every two weeks thereafter until the study completion. Safety data collection begins during baseline.

E. Reviewer of Data

The medical data will be reviewed by the Drs. Zimmerman-Bier, Gaffney, and London on a weekly basis. Behavioral data will be reviewed by Drs. London and Yoo on a weekly basis.

The PI and Co PI's will meet monthly at the start of the study and then quarterly to discuss the study progress.

We will be using an independent Data and Safety Monitoring Board (DSMB) to ensure the safety of research participants and the integrity of the study data. The DSMB is comprised of experts in clinical trials, statistics, pharmacology and autism. They have no direct relationship with the study. The DMSB will meet quarterly or as needed ad hoc to monitor the progress, efficacy, safety, and other confidential data from this study.

Data Type	Frequency of Review	Reviewer
Adherence to protocol	Quarterly	PI, co-PI, DSMB
Status of all enrolled subjects, as of date of reporting	Quarterly	PI, co-PI, DSMB
Adherence regarding study visits and med compliance	Quarterly	PI, co-PI, DSMB
Medical and Behavioral AEs & SAEs	Per Occurrence	PI, co-PI, DSMB

F. Schedule Of Review Of Cumulative Data

The PI will meet with the RA bi weekly to discuss and review the study progress. This will include screening data, outreach and recruitment. The PI will review study documents, informed consent, data acquisition and any safety issues (e.g., failed cardiac screening or participant adverse events). The PI will review the RA progress in task completion and develop plans to meet the study ongoing needs.

The PI and Co PI will meet quarterly to discuss the study including challenges and accomplishments. Each member will provide updates on the study. The results of the DSMB quarterly analysis will be reviewed by each member of the team.

G. Tests for Safety Data

The DSMB review will be centered in systematic analysis of Adverse Events (AEs) and Serious Adverse Events (SAEs). The DSMB review will analyze the Adverse Events (AEs) and Serious Adverse Events (SAEs) including their occurrence, grading, and causality. The Board will consider dropout rates and reasons, hypothesis validation, analysis of outcome data, and its relationship to potential modifications in study design and procedures, and participant complaints, in their written safety reports. Monitoring adverse effects and a sequential stopping rule may be formed in two ways:

1) Bayesian approach to evaluating the proportion of participants with side effects
2) Hypothesis testing approach using the sequential probability ratio test to see if the normal, acceptable side effect rate has been exceeded.

H. Suspension of Research

This study will be stopped prior to its completion if: (1) propranolol is associated with adverse effects that call into question the safety of the intervention; (2) any new information becomes available during the trial that necessitates stopping the study; or (3) other situations occur that might warrant stopping the study.

6.4 Reporting Results

A. Sharing of Results with Subjects
The study results will be shared with each participant and his/her parent or legally acceptable representative. The results will be conveyed by the study psychiatrist at the termination of the double-blind study.

B. Individual Results
We will have a standard plan in which the investigators offer to share individual behavioral results with each participant and his/her parent or legally acceptable representative.

C. Aggregate Results
We will also share a summary of findings with all participants or those who express an interest in receiving a summary. The results will be conveyed by the study psychiatrist at the termination of the double-blind, placebo-controlled cross-over portion of the study (i.e., prior to open label).

D. Professional Reporting

Preliminary research analysis and project related progress will be shared with the New Jersey Governor's Council for Medical Research and Treatment of Autism in quarterly and annual reports and research meetings. We will disseminate our research findings at professional meetings and publications in discipline-related journals.

E. ClinicalTrials.Gov Registration And Data Reporting

This study will be registered at clinicaltrials.gov

6.5 Secondary Use of the Data

We do not have definitive plans to share the data for secondary research, however, we have included language in the consent form for permission to use de-identified data from subjects for analysis by other researchers.

7.0 Data and/or Specimen Banking

N/A

8.0 Other Approvals/Authorizations

Because the study co-investigators (Eric London, J. Helen Yoo) are employed at the New York State Institute for Basic Research (IBR), this study will be reviewed by the Office of Research Oversight of the

New York State Psychiatric Institute and the Department of Psychiatry of Columbia University: https://irb.nyspi.org/ . Pending Rutgers IRB approval, Psychiatric Institute and the Department of Psychiatry of Columbia University IRB has indicated that they would agree to cede the review to Rutgers IRB.
The Office of Corporate Compliance has determined that a Data Use Agreement is not needed for Drs. Yoo and London. (see email)

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