Study Protocol:
A Pilot Study of Oxytocin for the Treatment of Social Impairment in Individuals with High Functioning Autism Spectrum Disorder

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IND Number: 133492

Version Date: CR 2 RtR 1, submitted to the IRB: 05/01/2019
Last Modified: 05/01/2019

1. BACKGROUND AND SIGNIFICANCE

Autism Spectrum Disorder (ASD) is estimated to affect up to 1.5% of youth in the general population (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2010). Deficits in social interaction are the central feature of ASD, and to date there is no pharmacological treatment available to address it.

Oxytocin (OT) is a pro-social neuropeptide hormone that has been reported to have a powerful role in affiliative behaviors in both humans and other mammals. OT plays a role in the formation of trust in humans (e.g. Kirsch et al., 2005, Baumgartner et al., 2008), in promoting social behavior in other animals (Williams et al., 1994), and has been shown to improve 'mind-reading' (ToM) performance in healthy people (Domes et al., 2007). This hormone is of particular interest because several gene-linkage studies in different cultural cohorts have shown an association between several single-nucleotide polymorphisms associated with OT and risk for ASD (Jacob et al., 2007; Liu et al., 2010). Acute OT administration improved accurate recognition of affect in speech in ASD (Hollander et al., 2007), decreased repetitive behaviors (Hollander et al, 2003), and increased the proportion of time that ASD participants spent looking at the eyes in static pictures of faces (Andari et al., 2010). In animal models, OT receptor knockout mice show social recognition deficits (Ferguson et al., 2000; Takayanagi et al., 2005) and, OT administration into the central amygdala appears to reverse these deficits (Ferguson et al., 2001).

Recent studies investigating chronic intranasal oxytocin administration suggest that the treatment is safe and well tolerated amongst youths and adults with ASD (Guastella et al., 2015; Tachibana M et al., 2013; Anagnostou et al., 2012). In a total 5-month trial (8-week randomized-controlled trial [RCT] followed by 3-month open-label trial [OLT]) of daily administration of oxytocin (24 IU BID) was well tolerated by adolescent males with ASD (N=26; ages 12-18) (Guastella et al., 2015). A 6-week RCT that examined the safety and efficacy of daily administration of intranasal oxytocin (24 IU BID) in adults with ASD (N=19; ages 19-46) reported no significant, serious, or treatment-limiting adverse events (Anagnostou et al., 2012). Results of such recent research indicate that chronic oxytocin administration in youth and adults with ASD is both safe as well as promising and that future studies are warranted to continue to evaluate the efficacy of chronic oxytocin treatment for social impairment amongst individuals with ASD.

2. SPECIFIC AIMS

This proposal seeks to examine the short-term efficacy and tolerability of intranasal oxytocin for the treatment of social impairment in youths and adults with high-functioning ASD (HF-ASD). We will be conducting a prospective, open label 8-week pilot trial with oxytocin nasal spray (Syntocinon). Based on the literature and our previous work, we hypothesize that oxytocin will be safe, tolerable, and effective in improving social deficits in individuals with ASD. We propose to enroll 30 youth 12-17 years of age and 30 adults 18-55 years of age of both sexes with HF-ASD.

3. LENGTH OF STUDY

Total duration of participation from enrollment to completion in this 8-week OLT of OT may take up to 11 weeks (allowing up to three weeks from date of consent to schedule and complete the baseline (week 0) visit). Subjects will be assessed on measures of efficacy and safety at the baseline (week 0), midpoint (week 4), and endpoint visits (at completion (week 8) or early termination).

4. SOURCE OF SUBJECTS

In order to achieve the goal of exposing 40 subjects to the study medication, we anticipate to consent up to 60 individuals with HF-ASD. Participants will be recruited from the referral pool of existing ASD patients within the Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD, the Division of Child and Adolescent Psychiatry, as well as the Bressler MGPO practice at MGH.

If a potential subject's clinician ascertains that the patient has an interest in study participation, the clinician will offer contact information for the study coordinator to the patient and their parents/guardian(s). The patient and their parent/guardian can then contact the study coordinator for more information on the trial. Further, the subject's clinician may also provide the contact information of interested, prospective participants to the study coordinator so that (s)he may recruit and communicate with perspective subjects via telephone calls and email. Any email communication with subjects will be done using encrypted email (i.e. "Send Secure"), unless the subjects opt to receive non-encrypted email. The benefits on encrypted emails will be explained to subjects. All participants, upon attaining the consent and/or assent by a clinician other than the patient's treating clinician, will undergo standard screening procedures. Participants who meet the study inclusion criteria and no study exclusion criteria will be offered to initiate the OT trial.

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

5. SUBJECT ENROLLMENT

Informed consent/assent will be obtained prior to administering study related procedures and drug treatment. The informed consent and assent documents will be used to explain, in simple terms, the risks and benefits of study participation to the subject and, if the subject is between the ages of 12 and 17, their parent/guardian. Subjects ages 12-17 will provide written assent. Subjects ages 14-17 will sign the same consent form as the parent, while subjects ages 12-13 will sign a separate assent form. If a subject turns 18 years old during the course of this study, he/she will be asked to sign the consent form again as an adult before continuing with the study. If the subject refuses to provide written consent after attaining majority status, he/she will be discontinued from the study. For subjects over 18, informed consent for self-participation will be obtained. The nature of the study will be fully explained to the subject and their parent/guardian by a study clinician other than the subject's treating physician, who is either the principal investigator or a co-investigator. The subject and their parent/guardian will be encouraged to ask questions pertaining to their participation in the study and the subject and their parent/guardian may take as much

time as they feel necessary to consider their participation in the study and to consult with family members or their physician. Participation in this study is entirely voluntary, and the subjects and/or their caretaker may withdraw from the study at any time for any reason. The IRB-approved informed consent/assent documents will be signed and dated by the subject and the physician obtaining consent**.**

6. SUBJECT SELECTION CRITERIA

A. Inclusion Criteria

1. Male and females between 12 and 55 years of age.
2. Meets DSM-5 diagnostic criteria for ASD as established by clinical diagnostic interview and the MGH ASD Symptom Checklist.
3. At least moderate severity of ASD impairment as measured by a raw score of ≥85 on the SRS.
4. Participants and their parent/guardian must be able to speak and understand English sufficiently to comprehend the nature of the study and to allow for the completion of all study procedures required per protocol.
5. Subjects and their parent/guardian must be considered reliable reporters. They must understand the nature of the study and must sign an IRB-approved informed consent form before initiation of any study procedures. Subjects and their parent/guardian must have a level of understanding sufficient to communicate with the investigator and study coordinator, and to cooperate with all tests and examinations required by the protocol.
6. Each subject and their parent/guardian must understand the nature of the study and provide written informed assent/consent.
7. Subjects with mood, anxiety, or disruptive behavior disorders will be allowed to participate in the study provided they do not meet any exclusionary criteria.
8. Subject must be willing to restrict concomitant usage of any intranasal medications.
9. If the subject is sexually active, he/she must agree to use an acceptable form of birth control during the study. These include:
    - Abstinence (no sexual contact)
    - A barrier method (diaphragm plus spermicide or a condom plus spermicide) in addition to one of the following methods:
        - Consistent use of an approved birth control pill
        - Birth control patch
        - Injected contraceptives
        - Intrauterine device (IUD)

B. Exclusion Criteria

1. Impaired intellectual functioning and/or impaired spoken language.
2. Clinically unstable psychiatric conditions or any serious medical illness, which will be assessed by study clinicians during the psychiatric interview and medical history review. If the clinical assessment suggests a psychiatric or medical condition demanding acute clinical attention, then the subject will be excluded from participating in the trial.

3. Pregnant or nursing females.
4. Known hypersensitivity to oxytocin.
5. Severe allergies or multiple adverse drug reactions.
6. A non-responder or history of intolerance to oxytocin, after treatment at adequate doses as determined by the clinician.
7. Subjects with significant nasal pathology (including atrophic rhinitis, recurrent nose bleeds, and history of hypophysectomy).
8. Clinically abnormal baseline laboratory values falling significantly outside of the standard reference ranges for a basic metabolic screen that jeopardize safe participation in the trial as determined by study clinician.
9. Investigator and his/her immediate family defined as the investigator's spouse, parent, child, grandparent, or grandchild.
10. Currently enrolled or recently participated (within the past 6 months) in a clinical trial of intranasal oxytocin.

7. DESIGN

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

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

Primary outcome measure of efficacy will be reduction in ASD symptom severity as measured by change from baseline raw score on the SRS. Responders will be defined as ≥30% reduction in SRS raw score. Safety and tolerability will be assessed by the monitoring of treatment-emergent adverse events by the participant's treating clinician**.** In the event that a participant's treating clinician is unavailable to assess safety and tolerability for a particular study visit, the participant will be scheduled with another study clinician who will conduct the safety and tolerability monitoring.

Dosing

Test Dose: Participants found eligible to participate in the trial will receive a test dose of oxytocin at the baseline visit (week 0). The test dose of 24 IU will be administered intranasally by the study clinician in order to: 1) demonstrate to patients and their parents the proper administration technique of the study medication; and 2) ensure that subject is able to tolerate intranasal administration. Participants who tolerate the single dose of oxytocin will participate in the 8-week chronic administration oxytocin trial if they so choose (see details on pages 8 & 9).

8-week OLT: Over the course of the 8-week study, participants will be evaluated at 4 week intervals. First at the baseline visit, at the midpoint study visit (week 4, and at the endpoint study visit (at completion [week 8] or upon early termination). At each visit, assessment measures of safety and efficacy will be administered and subjects will be evaluated for response to the treatment and adverse events.

The oxytocin will be administered in twice daily divided dosages with a total daily dose of 48 IU/day. A 24 IU administration of the oxytocin will be administered in the morning and afternoon to achieve the 48 IU daily dose. Each spray (puff) contains 4 IU of oxytocin, thus a full 24 IU dose will consist of 3 puffs per nostril. There will be an option for lowering the dose based on tolerability and response to oxytocin per clinician judgment. Study clinicians will be available 24 hours a day/7 days a week by pager in the event of any adverse reactions.

To assess and ensure drug accountability and compliance, study medication will be returned at every visit. Study staff will remind subjects to return all study medication bottles when contacting subjects to confirm their next study visit. Additionally, study staff will emphasize the importance of returning study medication when dispensing the medication to subjects. Because the study medication is in the form of a nasal spray, it is difficult to physically calculate medication compliance. Subjects or their parent/guardian will be asked to keep a medication log to record the amount of nasal spray administered, as well as the time of each administration. Subjects will be reminded to bring this medication log with them to each study visit along with their study medication.

Concomitant Medications/Treatments

At each study visit, subjects will be assessed for the use of concomitant medication. The guidelines for use of concomitant medications/treatments during the study are as follows:

- Concomitant administration of carboprost, dinoprostone vaginal gel/insert, ephedra, ephedrine, or direct sympathomimetics will **not** be allowed.
- Subjects may maintain treatment with psychotropic medications throughout the study, provided that they have been on a stable regimen for at least 3 weeks prior to baseline.
- Non-pharmacological treatments such as supportive individual, family, or group therapy will be permitted provided they were in place for at least 3 weeks prior to study enrollment and remain unchanged during the course of the trial.

Screening Process (Week 99)

Before any participant can start the study, the study physician will discuss the details of the study with the participant and their parent/guardian. No study procedures will be initiated before the participant agrees to participation and provides written consent in the case of an adult (ages 18-55) or the participant and the participant's parent/guardian

agrees to participation and provides written consent in the case of a minor (ages 12-17) as well as written assent for participants ages 12-13 years.

The screening process, including the process of attaining informed consent/assent, will take 1-2 hours in total and includes the following components:

- Subjects will meet with a study clinician for a psychiatric interview and review of medical history.
- The clinician will complete the MGH ASD Symptom Checklist. If this form has been completed by a clinician within the past year prior to a subject's entrance into this study, we will use the previously collected data so as to not burden the subject with redundant time commitments.
- Female participants of childbearing potential will complete a urine pregnancy test. If a participant has a positive pregnancy test, she will not be able to take part in the study. The study physician will inform the participant and discuss the clinically appropriate course of action. The decision whether to inform the participant's parent/guardian of these results will be made by the study physician based on the participant's age and maturity level. The participant will be offered 3 follow-up visits.
- Participants will be required to give a urine sample to test for illicit drugs. If the results are positive for drug(s), subjects will not be allowed to participate in this trial.
- About 1 tablespoon of blood will be drawn for laboratory tests. Clinical laboratory testing will consist of a basic metabolic panel (electrolytes, liver function tests, and glucose). Vital signs (blood pressure, heart rate, height, and weight) will be collected. The basic metabolic panel consists of the following tests: Na, K, Cl, CO2 (bicarb), BUN, Glucose, Creatinine, and Calcium.
- For subjects ages 12-17:
    - We will ask the subject's parent/guardian to fill out a questionnaire about the subject's ASD symptoms (SRS-2 School Age) as well as a brief demographic questionnaire collecting information regarding socioeconomic status and history of head injury or trauma. These questionnaires will take approximately 25 minutes to complete.
- For subjects ages 18-55:
    - We will ask subjects to fill out a questionnaire about their ASD symptoms (SRS-2 Adult Self-Report) as well as a brief demographic questionnaire collecting information regarding socioeconomic status and history of head injury or trauma. These questionnaires will take approximately 25 minutes to complete
        - Optional: If an informant for the participant is available, (s)he will be asked to fill out a scale about the subject's severity of autism spectrum symptoms (SRS-2 Adult Informant). This will take approximately 20 minutes to complete.

If a subject and/or informant has completed any of the above scales (SRS-2 School Age, SRS-2 Adult Self-Report or the demographic questionnaire) for another study within the Clinical and Research Programs in Pediatric Psychopharmacology and Adult

ADHD (or through his/her clinical care within these programs), the Division of Child and Adolescent Psychiatry, or through the Bressler MGPO practice at MGH within the past 6 months prior to a subject's entrance into this study, they will not be asked to repeat them at the week 99 screening visit. We will use the previously collected study assessment data so as to not burden the subject with redundant time commitments. However, the study clinician will review the interval time period to assess for clinically significant medical or psychiatric history to ensure that the subject meets appropriate study entrance criteria.

Office Study Visits (Weeks 0, 4, and 8)

Study visits will have a visit window of +/- 5 days to facilitate scheduling.

During study visits:

- A study doctor will ask the participant questions about the participant's ASD symptoms as well as general and mental health.
- The study physician will ask if the participant is having any side effects, and if they have taken any other medications during the previous week (see Table I for details).
- We will measure participant's blood pressure, heart rate, and weight.
- We will ask the participant for a urine sample in order to test for illegal drugs. We will do this at Weeks 4 and 8.
- We will ask for a urine sample to test for pregnancy for female participants of childbearing potential. We will do this at Weeks 4 and 8.
- During the final study visit (Week 8), we will obtain blood for a basic metabolic screen. The total amount of blood drawn during this study is about 2 tablespoons.
- For participants ages 12-17:
    - At weeks 4 and 8, we will ask the participant's parent/guardian to fill out the SRS-2 School Age form. This will take about 15 minutes.
    - At week 0 and week 8, we will also ask the participant's parent/guardian to fill out questionnaires about the subject's emotional functioning (CBCL) and quality of life (PQ-LES-Q). These questionnaires will take approximately 20 minutes to complete.
    - At weeks 0, 4, and 8, we will ask the participant's parent/guardian to fill out the MGH Social-Emotional Competence Scale (Informant-Rated Measure) (MGH-SECS-I). This will take about 10 minutes.
- For participants ages 18-55:
    - At weeks 4 and 8, we will ask participants to fill out the SRS-2 Adult Self-Report. This will take approximately 15 minutes.
    - At week 0 and week 8, we will also ask participants to fill out questionnaires about their emotional functioning (ASR), and quality of life (Q-LES-Q). These questionnaires will take approximately 20 minutes to complete.
    - At week 4 and 8, if an informant for the participant is available, (s)he will be asked to fill out a questionnaire about the subject's severity of autism spectrum symptoms (SRS-2 Adult Informant). This will take approximately 15 minutes to complete.

- At weeks 0 and 8, if an informant for the participant is available, (s)he will be asked to fill out a questionnaire about the subject's emotional functioning (ABCL). This will take approximately 10 minutes to complete.
- At weeks 0, 4, & 8, if an informant for the participant is available, (s)he will be asked to fill out the MGH-SECS-I. This will take approximately 10 minutes to complete.

Phone Study Visit (Week 2)

This study visit will have a visit window of +/- 5 days to facilitate scheduling.

During this study visit:

- A study doctor will call the participant and ask them questions about the participant's ASD symptoms as well as general and mental health.
- The study physician will ask if the participant is having any side effects, and if they have taken any other medications during the previous week (see Table I for details).

Study Discontinuation

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

- Subjects who experience intolerable adverse effects, and/or clinically significant laboratory values inconsistent with continuation in the study as determined by the PI.
- Worsening of psychiatric or medical illness as determined per clinical assessment or as reflected by Clinical Global Improvement score of 6 (Much worse) or 7 (Very much worse) for 2 visits in a row.
- Unstable psychiatric condition that clinically requires 1) treatment with prohibited concomitant psychotropic medications or 2) subjects requiring inpatient psychiatric admission.
- Emergent suicidality in the opinion of the investigator or as evidenced by a "yes" to questions 4 and/or 5 of Columbia-Suicide Severity Rating Scale (C-SSRS) within the last 1 month.
- Active substance abuse
- Pregnancy
- Allergic drug reaction
- Non-compliance (less than 70% compliance for 2 visits or longer based on parent report)
- Failure to keep study appointments for more than 2 consecutive visits without justification
- Clinical judgment of the investigator
- Withdrawal of consent

Those subjects who terminate study participation before the completion of the study will be asked to complete all tasks scheduled to take place on the final study visit at the time of study discontinuation.

Subjects who fail to keep study appointments or are non-compliant based on parent/self report (less than 70% compliance for two weeks or longer) may be dropped from the study. These study subjects will resume their clinical care with their respective treating clinician.

Subjects recruited from the Principal Investigator or Co-Investigator's own patient pool who drop out of the study prior to completion of the study will resume their care with their respective treating clinicians. If a subject chooses to drop out of the study, his or her clinical care now and in the future will not be affected. At study completion, subjects who complete the study will also resume their care with their respective treating clinicians.

If study participation is discontinued for safety reasons, participants will be offered three follow-up clinical visits, allowing adequate time for appropriate psychiatric referrals to treaters in their communities.

8. ASSESSMENTS (See Table I for an assessment schedule)

Study Rating Scales

Participants ages 12-17:

(Administered at screening evaluation)

- Social Responsiveness Scale: Second Edition School Age (SRS-2 School Age) is a 65-item rating scale completed by parent or guardian that is used to measure the severity of autism spectrum symptoms as they occur in natural settings (Constantino & Gruber, 2012).
- Demographic Questionnaire is a brief demographic questionnaire administered to subject's parent/guardian to estimate socioeconomic status, as well as collect information about any educational accommodations and past head injuries and/or trauma (Hollingshead, 1975).

(Administered at baseline [week 0] and final study visits [week 8/drop visit])

- Child Behavior Checklist (CBCL) is a parent-report questionnaire that evaluates maladaptive behavioral and emotional problems, both internalizing and externalizing, in children ages 6-18 (Achenbach, 2001).
- Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) is a self/parent/guardian-report measure that assesses quality of life from the subject's perspective (Endicott et al., 2006). Subjects or parents/guardians are instructed to consider each item and indicate their response on a scale of 1-5.

(Administered at midpoint [week 4] and final study visits [week 8/drop visit])

- Social Responsiveness Scale: Second Edition School Age (SRS-2 School Age) is a 65-item rating scale completed by parent or guardian that is used to measure the severity of autism spectrum symptoms as they occur in natural settings (Constantino & Gruber, 2012).

(Administered at baseline [week 0], midpoint [week 4], and final study visits [week 8/drop visit])

- MGH Social-Emotional Competence Scale (Informant-Rated Measure) (MGH-SECS-I) is a 37-item scale that asks informants to rate subjects on their social competence and abilities on a Likert scale from 0 to 6.

Participants ages 18-55:

(Administered at screening evaluation)

- Social Responsiveness Scale-Second Edition Self-Report (SRS-2 Adult Self-Report): a 65-item rating scale completed by subjects that is used to measure the severity of autism spectrum symptoms as they occur in natural settings (Constantino & Gruber, 2012).
- Demographic Questionnaire is a brief demographic questionnaire administered to the subject to estimate socioeconomic status, as well as collect information about any educational accommodations and past head injuries and/or trauma (Hollingshead, 1975).

(Administered at baseline [week 0] and final study visits [week 8/drop visit])

- Adult Self Report (ASR) is a self-rated questionnaire that evaluates maladaptive behavioral and emotional problems, both internalizing and externalizing, in adults ages 18-59 (Achenbach, 2003).
- Quality of Life Enjoyment and Satisfaction Questionnaire *(Q-LES-Q*): a 16-item questionnaire to evaluate the degree of enjoyment and satisfaction experienced in eight areas of daily functioning (Endicott, Nee et al. 1993).
- Adult Behavior Checklist (ABCL) is an informant-rated assessment of adult behavior, social competence, and substance use (Achenbach & Rescorla, 2003)

(Administered at screening evaluation, and midpoint [week 4] and final study visits [week 8/drop visit])

- Social Responsiveness Scale-Second Edition Informant-Report (SRS-2 Adult Informant): a 65-item rating scale completed by parents/caregivers that is used to measure the severity of autism spectrum symptoms of the subjects as they occur in natural settings (Constantino & Gruber, 2012).

(Administered at baseline [week 0], midpoint [week 4], and final study visits [week 8/drop visit])

- MGH Social-Emotional Competence Scale (Informant-Rated Measure) (MGH-SECS-I): is a 37-item scale that asks informants to rate subjects on their social competence and abilities on a Likert scale from 0 to 6.

Clinician-Rated:

Diagnostic

- *MGH Autism Spectrum Disorder DSM-5 Diagnostic Symptom Checklist (MGH-ASD-SCL)*: The range and severity of subjects' ASD symptoms will be assessed with the clinician-administered MGH-ASD-SCL. This screening instrument adopted items from DSM-5 diagnostic criteria for ASD and assesses for the individual core domains and associated features of ASD.

Safety

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

Rating Scales

- *Columbia-Suicide Severity Rating Scale (C-SSRS):* to assess previous suicidality of a subject at screening as well as any new instances of suicidality during the study.
- *Clinical Global Impression Scale (CGI):* The CGI is a measure of illness severity, improvement, and efficacy of treatment. The score for severity ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill subjects). Improvement ranges from 1 (very much improved) to 7 (very much worse). And lastly, the effectiveness index measures to what extent the subject is experiencing therapeutic effects as well as the level of adverse events they are experiencing. The CGI scale will be used for the assessment of ASD (NIMH, 1985).

9. DATA ANALYSIS

Statistical Analysis

Considering this study's open-label single group design, we will rely on comparisons of participants' performances at baseline (Week 0) prior to the initiation of treatment relative to their scores at the last assessment (Week 8 or drop). Thus, statistics for paired samples will be utilized. This design largely protects against the bias introduced by confounding factors. That is, since the same participants are tested on two occasions, all static confounding factors are perfectly balanced, and can have no impact on the findings. Bias can still result from time-varying factors that are not associated with the outcomes, but we are confident that any such factors will have a minimal impact on this study, considering the duration of the trial. Specifically, we will employ Wilcoxon signed rank tests for continuous or discrete outcome measures, and McNemar's test for binary outcomes. These tests are free from assumptions regarding the distribution of the outcome variables, which is appropriate since the scales we are proposing to utilize are not considered to have Gaussian distributions, and will not be amenable to parametric methods.

10. SAFETY

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

If a subject is withdrawn from the study due to adverse events, lack of response, or as a decision by the clinician, they will be offered open treatment for three months,

giving adequate time for appropriate psychiatric care to be arranged.

Blood Draw

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

Study Medication

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

11. CONFIDENTIALITY

All research-related records initiated as a result of a subject's participation in this study that reveal the subject's identity will remain confidential except as may be required by law. While the results of the clinical laboratory blood testing will become part of a subject's Massachusetts General Hospital medical record, they will not link the subject to participation in any research. Subjects will only be contacted regarding future studies if they indicate that they are interested in being contacted by initialing in the specific section of the consent form.

12. RISKS AND DISCOMFORTS

Syntocinon nasal spray is not FDA-approved for any indication. Syntocinon injection is indicated for medical (rather than elective) induction of labor. As was mentioned in the Background and Significance section, in recent clinical trials involving intranasal oxytocin administration in humans, the risks of oxytocin have been mild and rare. A review of the safety, side effects, and case-by-case reactions to intranasal oxytocin examined 38 randomized controlled trials in which 8% of participants met diagnostic criteria for a developmental or mental health disorder (MacDonald et al., 2011). The review corroborated the aforementioned recent research findings as side effects of intranasal oxytocin were mild—reported side effects included increased calmness/euphoria, feeling more comfortable or having more energy, light headedness, drowsiness and/or headache, nasal irritation, and dry mouth/throat. The researchers concluded that the evidence showed that intranasal oxytocin produced no reliable side effects and was not associated with adverse outcomes when delivered in doses of 18-40 IU for short-term use.

Chronic administration of oxytocin (24 IU BID) was well tolerated by adolescent males with ASD (N=26; ages 12-18) (Guastella et al., 2015). The number of side effects reported did not differ between placebo and oxytocin groups at any point during the trial. No serious adverse events resulted from oxytocin treatment compared to placebo. In a

long-term open label study in which youth males (N=8; ages 10-14) received daily intransal oxytocin in a stepwise increased dosage manner every 2 months (8, 16, 24 IU/dose), all participants reported no side effects (Tachibana M et al., 2013). Side effects in this trial were assessed by monitoring blood pressure and examining urine and blood samples. A 6-week RCT that examined the safety and efficacy of daily administration of intranasal oxytocin (24 IU BID) in adults with ASD (N=19; ages 19-46) reported no significant, serious, or treatment-limiting adverse events (Anagnostou et al., 2012). There were no significant differences observed between oxytocin and placebo groups in any blood results and no abnormal electrocardiograms were reported. Results of such recent research indicate that chronic oxytocin administration in youth and adults with ASD is both safe as well as promising and that future studies are warranted to continue to evaluate the efficacy of chronic oxytocin treatment for social impairment amongst individuals with ASD.

Frequent Adverse Events

The most frequently observed adverse reactions to oxytocin nasal spray (Syntocinon) are abnormal uterine contractions, headache, nausea and dermatitis allergic. The frequency of nasal discomfort associated with administration of Syntocinon is not known. Less frequently observed adverse reactions include mild to moderate increases in irritiability, mild fatigue, headache, leg shaking, and increased energy (Anagnostou et al., 2012). The evidence to date suggests that administering oxytocin intranasally does not increase the risks associated with the drug product.

All participants will be closely monitored for serious adverse reactions. All serious unexpected adverse events will be reported to the Partners Human Research Committee as stipulated by PHRC regulations.

Other Adverse Events

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

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

For all subjects and their parent/guardian, there is a risk of inconvenience and potential discomfort for filling out rating scales and questionnaires. All of the information about participants will be treated confidentially. Subjects and their parent/guardian can choose not to answer any questions that they do not feel comfortable answering.

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

13. POTENTIAL BENEFITS

There may be no direct benefit to subjects participating in this study. Participants may potentially benefit by experiencing improvement in social impairments and by gaining knowfledge about ASD.

Table I. Study Schema

	99	0	2	4	8
Consent/Assent	X				
Procedures					
Test Dose		X			
Blood Draw	X				X
Vital Signs (weight, BP, pulse)	X	X		X	X
Height	X				
Urine Drug Screen	X			X	X
Urine Pregnancy Test (WOCBP)	X			X	X
Clinician Rated Scales					
Psych Eval & Med History	X				
CTAE		X	X	X	X
Concomitant Medications	X	X	X	X	X
MGH ASD Checklist	X				
CGI-ASD-SI		X	X	X	X
CGI-ASD-SC		X	X	X	X
CGI-ASD-M		X	X	X	X
CGI-ASD		X	X	X	X
C-SSRS		X		X	X
Medication Log Review		X		X	X
Parent/Guardian Rated Scales					
Demograhic Questionnaire	X				
SRS-2 School Age	X			X	X
CBCL		X			X
PQ-LES-Q		X			X
MGH-SECS-I		X		X	X
Self Rated Scales (Ages 18-55)					
Demograhic Questionnaire	X				
SRS-2 Adult Self-Report	X			X	X
ASR		X			X
Q-LES-Q		X			X
Optional Informant Scale (Ages 18-					
MGH-SECS-I		X		X	X
ABCL		X			X
SRS-2 Adult Informant	X			X	X

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