HIC#1004006623

YALE UNIVERSITY SCHOOL OF MEDICINE
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Research

Please refer to the HIC website for application instructions and information required to complete this application. The Instructions are available at http://info.med.yale.edu/hic/forms/index.html. Submit the original application and two (2) copies of all materials including relevant sections of the grant which funds this project (if applicable) to the HIC.	**HIC OFFICE USE ONLY**	
	DATE STAMPED-RECEIVED	PROTOCOL NUMBER

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: Double-Blind, Placebo-Controlled Trial of N-acetylcysteine (NAC) for the treatment of Pediatric Obsessive-Compulsive Disorder in Children

Principal Investigator: Michael H. Bloch, M.D., M.S.		**Yale Academic Appointment:** Postdoctoral Research Fellow	
Campus Address: Child Study Center, 230 S. Frontage Rd, PO BOX 207900, New Haven, CT 06520			
Campus Phone: 203-974-7551	**Fax:** 203-785-7611	**Pager:** 203-745-9921	**E-mail:** Michael.bloch@yale.edu
Protocol Correspondent Name & Address (*if different than PI*): **Kaitlyn E. Panza, B.A.** Child Study Center, 230 S. Frontage Rd, PO BOX 207900, New Haven, CT 06520			
Campus Phone: 203-737-4809	**Fax:** 203-785-7611	**E-mail:** Kaitlyn.panza@yale.edu	

Faculty Advisor:(required if PI is a student, resident, fellow or other trainee) ☐ **NA** James F. Leckman, M.D.		**Yale Academic Appointment:** Professor	
Campus Address: Child Study Center, 230 S. Frontage Rd, PO BOX 207900, New Haven, CT 06520			
Campus Phone: 203-785-7871	**Fax:** 203-785-7611	**Pager:**	**E-mail:** James.leckman@yale.edu

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

APPROVED BY THE YALE UNIVERSITY IRB 3/17/2017 VALID THROUGH 4/15/2018

a. Internal Location[s] of the Study:

☐ Magnetic Resonance Research Center (MR-TAC)
☐ Yale Cancer Center
☐ Yale-New Haven Hospital
☐ PET Center
☐ YCCI/Church Street Research Unit (CSRU)
☐ YCCI/Hospital Research Unit (HRU)
☐ YCCI/Keck Laboratories
☒ Specify Other Yale Location: Yale Child Study Center, School of Medicine

b. External Location[s]:

☐ APT Foundation, Inc. ☐ Haskins Laboratories ☐ Connecticut Mental Health Center
☐ John B. Pierce Laboratory, Inc.
☐ Veterans Affairs Hospital, West Haven ☐ Other Locations, Specify:

c. Additional Required Documents *(check all that apply)*: ☐ N/A

☐ *YCCI-Scientific and Safety Committee (YCCI-SSC)	Approval Date:
☒ *Pediatric Protocol Review Committee (PPRC)	Approval Date:
☐ *YCC Protocol Review Committee (YRC-PRC)	Approval Date:
☐ *Dept. of Veterans Affairs, West Haven VA HSS	Approval Date:
☐ *Radioactive Drug Research Committee (RDRC)	Approval Date:
☐ YNHH-Radiation Safety Committee (YNHH-RSC)	Approval Date:
☐ Magnetic Resonance Research Center PRC (MRRC-PRC)	Approval Date:
☐ YSM/YNHH Cancer Data Repository (CaDR)	Approval Date:

☐ Dept. of Lab Medicine request for services or specimens form

Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities. 3-4 years.

3. **Targeted Enrollment:** What is the number of subjects

a. targeted for enrollment at Yale for this protocol? If this is a multi-site study, what is the total number of subjects targeted across all sites? Approximately 40 subjects all from Yale.
b. expected to sign the consent form? 40 subjects
c. expected to complete some or all interventions for this protocol? 40 subjects

4. **Research Type/Phase: (Check all that apply)**

a. **Study Type**

☒ Single Center Study
☐ Multi-Center Study
Does the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☐
☐ Coordinating Center/Data Management
☐ Other:

b. **Study Phase** ☐ **N/A**

☒ Pilot ☐ Phase I ☐ Phase II ☐ Phase III ☐ Phase IV
☐ Other (*Specify)*

c. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more

than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

☒ Clinical Research: Patient-Oriented
☐ Clinical Research: Epidemiologic and Behavioral
☐ Translational Research #1 ("Bench-to-Bedside")
☐ Translational Research #2 ("Bedside-to-Community")
☐ Clinical Research: Outcomes and Health Services
☐ Interdisciplinary Research
☐ Community-Based Research

5. Is this study required to be registered in a public database? Yes☒No ☐
   If yes, where is it registered?
   Clinical Trials.gov registry ☒
   Other (*Specify*)

6. Will this research study utilize clinical care services at Yale New Haven Hospital or YMG?
Yes ☐ No☒
If yes, might these be billable to the subject, the sponsor, grant or other third party payer?
Yes ☐No ☐
If you answered "yes", please register this study in the IDX/GE system at
http://www.yalemedicalgroup.org/pfs/forms/10000/NewStudyRequest.pdf

7. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ___ No X

If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform?
N/A

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure?
N/A

c. Will a novel approach using existing equipment be applied?
N/A

If you answered "no" to question 7a, or "yes" to question 7b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.
N/A

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Funding Source:** Indicate all of the funding source(s) for this study. Check all boxes that apply. Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is "pending" at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note "Pending" in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

PI	Title of Grant	Name of Funding Source	Funding	Funding Mechanism
Michael Bloch	Double-blind, Placebo-Controlled Trial of N-acetylcysteine for Pediatric OCD	International Obsessive-Compulsive Disorder Foundation -- pending	☐ Internal ☒ External	☐ Grant-M# ☐ Contract#
			☐ Internal ☐ External	☐ Grant-M# ☐ Contract#
			☐ Internal ☐ External	☐ Grant-M# ☐ Contract#

2. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.**

	Name	Signature ***	Protocol-Related COI?	Affiliation
Principal Investigator	Michael H. Bloch, M.D., M.S.		☐ Yes ☒No	Child Study Center
Role: Co-investigator	James F. Leckman, M.D.		☐ Yes ☒ No	Child Study Center
Role: Co-investigator	Robert E. King, M.D.		☐ Yes ☒ No	Child Study Center
Role: Co-investigator	Christopher Pittenger, M.D.		☐ Yes ☒ No	CMHC, Psychiatry
Role: Co-investigator	Angeli Landeros-Weisenberger, M.D.		☐ Yes ☒ No	Child Study Center
Role: Study Personnel	Megan E. Smith, B.A.		☐ Yes ☒ No	Child Study Center
Role: Study Personnel	Kaitlyn E. Panza, B.A		☐ Yes ☒ No	Child Study Center

*****My signature here indicates that I have read, am in compliance with, and will continue to be in compliance with the HIC's Protocol-Specific Conflict of Interest policy and the University's policy on Conflict of Interest and Conflict of Commitment.**
NOTE: The HIC will remove from the protocol any personnel who have not signed the application and/or completed required training. A personnel protocol amendment will need to be submitted when training is complete or signature is provided.

SECTION IV: PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.

_____ _____

PI Name (PRINT) and Signature Date

As the **faculty advisor** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
- I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- The student investigator will obtain approval for this research study and any subsequent revisions Prior to initiating the study or revision and will obtain continuing approval prior to the expiration of any approval period.
- The student investigator will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set forth by the University and qualify to serve as the faculty advisor of this project.

_____ _____

Advisor Name (PRINT) and Signature Date

Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?
☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)
☐ No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?
☐ Yes, and I agree to submit the Protocol-Specific Conflict of Interest Disclosure Form.
☐ No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

_____ _____ _____
Chair Name (PRINT) and Signature Date

_____
Department

YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:
- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to submit a Protocol-Specific Conflict of Interest Disclosure Form if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and had the support of the hospital for this research project.

_____ _____ _____
YNHH HSPA Name (PRINT) and Signature Date

For HIC Use Only

_____ _____
Date Approved **Human Investigation Committee Signature**

SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.
   The aim of the study is to determine if N-acetylcysteine is an effective treatment for OCD in children.
2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Pediatric OCD affects 1-3% of children (Douglass, Moffitt et al. 1995; Zohar 1999). We currently have effective first-line interventions for pediatric OCD such as Cognitive Behavioral Therapy (CBT) and pharmacotherapy with serotonin reuptake inhibitors (SRIs) (POTS 2004). However, roughly half of children with OCD still have clinically significant OCD symptoms despite treatment with first-line pharmacological and CBT interventions for OCD (POTS 2004). When severe, OCD can be incapacitating with devastating consequences for children and their families. Augmentation strategies with antipsychotic medications can improve the effectiveness of SRI therapy but do not eliminate OCD symptoms (Bloch, Landeros-Weisenberger et al. 2006). Furthermore, all pharmacological treatments for OCD have an increased side effect burden when compared to adults. Novel treatments for children with OCD are needed.

Converging lines of evidence from neuroimaging, genetic and pharmacological studies support the importance of glutamate abnormalities in the pathogenesis of OCD (Rosenberg, MacMaster et al. 2000; Rosenberg, MacMillan et al. 2001; Chakrabarty, Bhattacharyya et al. 2005; Coric, Taskiran et al. 2005; Poyurovsky, Weizman et al. 2005; Arnold, Sicard et al. 2006; Dickel, Veenstra-VanderWeele et al. 2006; Lafleur, Pittenger et al. 2006; Pasquini and Biondi 2006; Pittenger, Krystal et al. 2006; Whiteside, Port et al. 2006; Stewart, Fagerness et al. 2007). In magnetic resonance spectroscopy studies, elevated concentrations of glutamate and related compounds have been demonstrated in the caudate nucleus and orbitofrontal cortex of OCD patients compared to normal controls (Rosenberg, MacMaster et al. 2000; Rosenberg, MacMillan et al. 2001; Whiteside, Port et al. 2006). Cerebral spinal fluid analysis has likewise demonstrated elevated glutamate levels compared to normal controls (Chakrabarty, Bhattacharyya et al. 2005). In genetic studies, single nucleotide polymorphisms within the glutamate transporter gene *SLC1A1* have been associated with the diagnosis of OCD (Arnold, Sicard et al. 2006; Dickel, Veenstra-VanderWeele et al. 2006; Stewart, Fagerness et al. 2007). Open-label, pharmacological treatment studies have suggested that glutamate modulating agents such as riluzole (Coric, Taskiran et al. 2005; Pittenger, Coric et al. 2008; Grant, Lougee et al. *in press*), N-acetylcysteine (NAC) (Lafleur, Pittenger et al. 2006) and memantine (Poyurovsky, Weizman et al. 2005; Pasquini and Biondi 2006) may be effective in the treatment of OCD. However, no double-blind, placebo-controlled trials of glutamatergic agents have been completed in OCD.

NAC is a naturally occurring amino-acid that has been used safely for decades as an antioxidant agent and as an antidote for acetaminophen overdose. Due to its benign safety profile, NAC is available as an over-the-counter medication at a cost of less than 25 cents a day. More recently, NAC has been demonstrated to be a glutamate modulating agent. NAC is converted to cystine, a substrate for the glutamate/cystine antiporter located on glial cells. The uptake of cystine by glia causes glial release of glutamate into the extrasynaptic space, where it appears to stimulate inhibitory metabotropic glutamate receptors on glutamatergic nerve terminals and thereby reduces the synaptic release of glutamate (Moran, McFarland et al. 2005). NAC has been recently demonstrated in randomized, double-blind, placebo-controlled studies to be effective for the treatment for bipolar depression and schizophrenia (Berk, Copolov et al. 2008; Berk, Copolov et al. 2008). NAC has also been demonstrated in double-blind, placebo-controlled studies to effectively reduce the symptoms of trichotillomania, a disorder that is considered to be on the OC spectrum and is often comorbid with OCD (Grant, Odlaug et al.

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2009). NAC has also demonstrated to be safe without significant side effects in a recent double-blind, placebo-controlled trial in children with autism (Posey, Erickson et al. 2009).

3. **Research Plan:** Provide an orderly scientific description of the study design and research procedures as they directly affect the subjects.

Subjects: Children with OCD will be recruited through the TS/OCD Clinic at the Yale Child Study Center. Inclusion and Exclusion Criteria are listed below.

Intervention: Subjects will be randomized in a ratio of 1:1 to receive treatment with NAC or placebo. NAC (or placebo) will be titrated up to a maximum dose of 2400mg/day over the course of 1 week. Subjects will take a single 600mg tablet twice a day for 1 week, and then increase to two 600mg tablets twice a day for the remainder of the 12 week study. After completion of the study all subjects receiving placebo will be offered NAC treatment for the following 12 weeks.

Subjects, their parents, investigators, staff, and persons performing the assessments will remain blind to treatment assignment from the time of randomization until their completion of the study after 12 weeks. Randomization data are kept strictly confidential until the time of unblinding and are accessible only to authorized persons. The identity of the treatments will be concealed by the use of study drugs that are identical in packaging, labeling, schedule of administration and appearance. Placebo and study drug will be prepared in a like fashion at the Yale-New Haven Hospital Investigational Drug Service pharmacy.

NAC is an altered form of the amino acid cysteine, which is commonly found in food and synthesized by the body. N-acetylcysteine (NAC) is generally well tolerated and has been extensively used in the treatment of acetaminophen overdose/toxicity at high doses for many years. The dosage in acute acetaminophen overdose is a 140mg/kg loading dose, followed by a maintenance dose of 70mg/kg administered every 4 hours for 17 consecutive doses. The dose used to treat acetaminophen overdose in children is approximately 10-fold greater than the maximum dose we will use in this study. Although generally well-tolerated, the PDR indicates that adverse reactions reported with oral NAC include nausea, vomiting, diarrhea, headache (especially when used along with nitrates) and rashes when used at higher doses (Cheng, Lin et al. 2007). There are rare reports of renal stone formation and cases of bronchospasm with intravenous use only. The long-term use of NAC has been well-studied in the treatment of Chronic Obstructive Pulmonary Disease and was extremely well-tolerated (Grandjean, Berthet et al. 2000). NAC has been well-tolerated in the treatment of adults with OCD and trichtillomania (TTM) at a maximum dose of 3000mg (Pittenger, Krystal et al. 2005; Lafleur, Pittenger et al. 2006).

Assessment: *Pre-study screening procedure:* After an initial phone screen to rule out obvious exclusions from the study protocol, potential subjects will have an initial evaluation that will be performed by a multidisciplinary clinical team. Exclusions in screening would include (1) Comorbid bipolar disorder, psychotic disorder, substance use disorder, developmental disorder or mental retardation (IQ<70), (2) asthma diagnosis requiring treatment in the last 3 months, and (3) a change in psychotropic medications or behavioral treatment for OCD within the last month. In addition to a standard clinical evaluation consisting of history, and mental status exams, subjects will receive a clinical diagnostic interview using the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) (Kaufman, Birmaher et al. 1997). Additional baseline ratings will be conducted for OCD, tic, depression and anxiety severity using: 1) Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) (Scahill, Riddle et al. 1997), (2) Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS).Additional baseline ratings

will be conducted for OCD, tics, trichotillomania, depression and anxiety severity using (3) Yale Global Tic Severity Scale (YGTSS) (Leckman, Riddle et al. 1989), (4) ADHD Rating Scale (ADHD-RS) (DuPaul, Power et al. 1998), (5) Multidimensional Anxiety Scale for Children (MASC) (March, Parker et al. 1997), (6) Children's Depression Inventory (CDI) (Kovacs 1985), (7) Massachusetts General Hospital – Hairpulling Scale (MGH-HPS) (Keuthen, O'Sullivan et al. 1995), (8) Clinical Global Impression (CGI) scale (Guy 1976) and (9) Pediatric-Adverse Events Rating Scale (PAERS) (March, Karayal et al. 2007). The pediatric adverse events rating scale will be used to monitor safety throughout the trial. A medical assessment including vital signs, physical exam and urine drug screen and pregnancy test will be completed prior to study enrollment. The measures utilized in this study are outlined below.

Baseline Assessments	**Medical Assessments**	**Rating scales**
K-SADS	Vital Signs	CY-BOCS DY-BOCS
Psychiatric History	Physical Exam	YGTSS ADHD-RS
General Medical History	Mental Status Exam	CDI MASC
	Urine Toxicology	MGH-HPS CGI
	Urine Pregnancy Test	PAERS

The table below indicates the clinical ratings scheduled planned for the trial. If subjects' have significant ADHD, tic, anxiety or depression symptoms at screening, ratings of these symptoms will be followed regularly at study assessments. Subjects will be encouraged to continue outside therapy and will be required to continue all concurrent medications during the course of this trial. Subjects will also be asked about the number of missed doses of medications at each study visit.

Measure	Screening/ Baseline	Week 2	Week 4	Week 8	Week 12
CY-BOCS	x	x	x	x	x
DY-BOCS	x	x	x	x	x
YGTSS	x		x	x	x
ADHD-RS	x		x	x	x
CDI	x		x	x	x
MASC	x		x	x	x
MGH-HPS	x		x	x	x
CGI	x	x	x	x	x
PAERS	x	x	x	x	x
NAC dose	600mg BID	1200 mg BID	1200 mg BID	1200 mg BID	1200 mg BID

3. **Statistical Considerations:** Describe the statistical analyses that support the study design.

We will use the CY-BOCS as our primary outcome measure. Our primary analysis will involve a mixed effects modelusing weekly CY-BOCS ratings from baseline to 12 weeks with treatment (NAC/placebo) as a fixed factor and time as a within-subject factor. We will adhere to intention-to-treat principles in our analysis. We powered our study to have 80% power to detect a large effect of NAC (d=0.9) assuming α=0.05. Given a similar variance in the Cy-BOCS scores in previous placebo-controlled trials of pediatric OCD, we would expect this effect size to correspond to a 6.5 point difference in Cy-BOOCS between the NAC and placebo groups (POTS

2004). By comparison, the effect size of NAC in the treatment of adults with trichotillomania, using the MGH-HS (d=1.2, N=50), and in bipolar depression, using the Montgomery-Asberg Depression Rating Scale (MADRS) (d=0.8, N=80) was considerably larger (Grant, Odlaug et al. 2008).

As a secondary outcome we will examine the safety and tolerability of NAC. Given our sample size of 40 we will have limited power to detect adverse events of low frequency. That being said, assuming that we do not see a side-effect in the placebo group, we will have 80% power to detect NAC related side-effect, if it occurs in one-third of NAC treated subjects. Frequency of side-effects will be measured with the PAERS as discussed in the assessments section.

SECTION VI: RESEARCH INVOLVING DRUGS, DEVICES, BIOLOGICS & PLACEBOS

1. **Identification of Drug, Device or Biologic:** What is (are) the **name(s)** of the drug(s), device(s) or biologic(s) being used? Identify whether FDA approval has been granted and for what indication(s).

N-Acetylcysteine (USP grade) is FDA approved for the pediatric population in oral form to reduce the extent of liver injury after an acetaminophen overdose. N-acetylcysteine (NAC) is an altered form of the amino acid cysteine, which is commonly found in food and synthesized by the body. NAC is generally well tolerated and has been extensively used at high doses in the treatment of acetaminophen overdose/toxicity for many years. The NAC dosage for acute acetaminophen overdose, in both adults and children, is a 140mg/kg loading dose, followed by a maintenance dose of 70mg/kg administered every 4 hours for 17 consecutive doses. The long-term use of NAC has also been investigated in six-month to three-year studies. These studies examine the efficacy and tolerability of NAC (dosed between 600-1200mg per day) in the treatment of chronic obstructive pulmonary disease COPD (Pela, Calcagni et al. 1999; Grandjean, Berthet et al. 2000; Stey, Steurer et al. 2000; Kasielski and Nowak 2001; Poole and Black 2001; Chikina, Iagmurov et al. 2002; Decramer, Rutten-van Molken et al. 2005). NAC helps the body synthesize glutathione, an important antioxidant. In animals, the antioxidant activity of NAC protects the liver from the adverse effects of exposure to several toxic chemicals. NAC also protects the body from acetaminophen toxicity and is used, at very high levels, in hospitals for patients with acetaminophen poisoning. It has also been shown to be effective at treating liver failure from causes other than acetaminophen poisoning (e.g., hepatitis, and other drug toxicity) and at preventing kidney damage caused by injections of iopromide, a contrast medium used in people scheduled to undergo computerized tomography (CT) imaging.

All protocols which utilize a drug, device or biologic **not** approved by, but regulated by, the FDA must provide the following information: ☒ **Not applicable to this research project**

i. What is the Investigational New Drug (IND) or Investigational Device Exemption (IDE) **number** assigned by the FDA?

ii. For IDE's: Did the FDA approve this IDE as a Category A (experimental/investigational) or as a Category B (non-experimental/investigational)?

iii. Who holds the IND or IDE?

The clinical investigation of a drug product that is lawfully marketed in the United States may be exempt from the requirements for filing an IND. If there is no IND and an exemption is being sought, complete the following:

i. Is the intention of the investigation to report to the FDA as a well controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug? ☐ Yes ☒ No
ii. If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, is the intention of the investigation to support a significant change in the advertising for the product? ☐ Yes ☒ No
iii. Does the investigation involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product? ☐ Yes ☒ No

The NAC dosage for acute acetaminophen overdose is a 140mg/kg loading dose, followed by a maintenance dose of 70mg/kg administered every 4 hours for 17 consecutive doses. The dose used to treat acetaminophen overdose in children is approximately 10-fold greater than the maximum dose we will use in this study.

iv. Will the investigation be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56)? ☒Yes ☐ No
v. Will the investigation be conducted in compliance with the requirements regarding promotion and charging for investigational drugs? ☒Yes ☐ No

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

N-acetylcysteine (NAC) is generally well tolerated and has been extensively used at high doses in the treatment of acetaminophen overdose/toxicity for many years. The NAC dosage for acute acetaminophen overdose is a 140mg/kg loading dose, followed by a maintenance dose of 70mg/kg administered every 4 hours for 17 consecutive doses. The long-term use of NAC has also been investigated in six-month to three-year studies examining the efficacy and tolerability of NAC (dosed between 600-1200mg per day) in the treatment of chronic obstructive pulmonary disease COPD (Pela, Calcagni et al. 1999; Grandjean, Berthet et al. 2000; Stey, Steurer et al. 2000; Kasielski and Nowak 2001; Poole and Black 2001; Chikina, Iagmurov et al. 2002; Decramer, Rutten-van Molken et al. 2005). A recent study by Decramer and colleagues in 2005 concluded that there were no adverse events thought to be drug related in their study examining the use of 600mg/day of NAC in over 500 patients with COPD. Additionally, Chikina and colleagues found that the most effective dose of NAC in the treatment of COPD was 1200mg/day (the study examined doses of NAC ranging from 600-2400mg/day). A meta-analysis examining the efficacy of NAC in COPD, performed in 2000, revealed that NAC was well tolerated without significant adverse effects (Grandjean, Berthet et al. 2000). Although generally well-tolerated, the PDR indicates that adverse reactions reported with oral NAC include nausea, vomiting, diarrhea, headache (especially when used along with nitrates) and rashes. There are rare reports of renal stone formation. It is also important to note that rare reports of bronchoconstriction have occurred with intravenous NAC (but no reports of bronchospasm related to the oral use of NAC). Although there are no known contraindications to

NAC use, individuals with asthma will be excluded from the study given the rare, but potential, adverse effect of bronchospasm.

The safety and tolerability of chronic NAC at higher doses has been evaluated in a number of contexts. In a double-blind, placebo-controlled randomized trial of oral NAC in HIV-infected patients, subjects were treated with 8,000mg per day of NAC for 8 weeks (De Rosa et al, 2000). Adverse effects in this trial were minimal and some subjects reduced the dose due to side effects, with the average dosage by the end of the trial being 6.3 grams/day; however, the reduction in "dose" was similar for the placebo arm. In another double-blind, placebo-controlled randomized trial involving 43 Alzheimer's patients, subjects were given placebo or 50 mg/kg/day orally (Adair, Knoefel et al. 2001). In that study, there were no adverse effects more common than in placebo (except perhaps headache).

In acetaminophen overdose, the dose of NAC is 140 mg/kg load followed by 70 mg/kg every 4 hours for 17 consecutive doses. At this dosage, NAC can cause nausea, vomiting and sometimes generalized urticaria. In normal volunteers the dose that the vast majority of patients were able to tolerate was 3200 mg/m2/day. Common toxicities at higher doses were bad taste and gastrointestinal disturbances (Pendyala and Creaven. et al).

Severe toxicity is rare and occurs at doses an order of magnitude higher than what we will be using in this study. In a single case report, a 16-kilogram child received 39,207 mg of intravenous NAC due to a medical error; she developed cerebral edema with uncal herniation (Bailey, Blais et al. 2004). The lethal oral dose of NAC is 4400 mg/kg in mice and 5050 mg/kg in rats (RTECS 2001).
According to the PDR: “NAC is rapidly absorbed from the gastrointestinal tract and transported to the liver via the portal circulation, where it undergoes extensive first-pass metabolism. Peak plasma concentrations are observed approximately 0.5 to 1 hour following oral administration of doses of 200 to 600 milligrams. NAC is metabolized to N-acetylcysteine, N, N-diacetylcystine and L-cysteine. L-cysteine itself is metabolized to glutathione, protein, taurine and sulfate. NAC has low bioavailability, probably because of its extensive first-pass metabolism in the liver. The terminal half-life of total NAC is approximately 6.25 hours after ingestion. Use of supplemental NAC along with carbamazepine may cause reduced serum levels of carbamazepine.”

NAC helps the body synthesize glutathione, an important antioxidant. In animals, the antioxidant activity of NAC protects the liver from the adverse effects of exposure to several toxic chemicals. NAC also protects the body from acetaminophen toxicity and is used at very high levels in hospitals for patients with acetaminophen poisoning. It has also been shown to be effective at treating liver failure from causes other than acetaminophen poisoning (e.g., hepatitis, and other drug toxicity) and at preventing kidney damage caused by injections of iopromide, a contrast medium used in people scheduled to undergo computerized tomography (CT) imaging.
Supplementation with NAC has been shown to reduce the proliferation of certain cells lining the colon and may reduce the risk of colon cancer in people with recurrent polyps in the colon.
There have been several case reports of oral NAC producing dramatic improvements in Unverricht-Lundborg disease, an inherited degenerative disorder involving seizures and progressive disability. One study used up to 3 grams of NAC per day.

Oral supplementation with NAC has been used successfully in two cases to treat a rare syndrome that complicates kidney dialysis. This condition, known as pseudoporphyria, has no other known treatment. Controlled clinical trials are needed to confirm these preliminary observations.

Our choice of using 2400 mg daily in this study stems from our preliminary experience with NAC in trichotillomania and refractory OCD (Lafleur, Pittenger et al. 2006; Grant, Odlaug et al. 2008). Although a dose of 2400mg has demonstrated efficacy for treating adults with TTM, higher doses of NAC are routinely used in the treatment of other psychiatric conditions. This dose has been well tolerated in this case report and in several other clinical observations (Pittenger, Krystal et al. 2005).

3. **Source:** a) Identify the source of the drug, device or biologic to be used.

N-Acetylcysteine will be obtained from the Yale-New Haven Hospital Investigational Drug Service pharmacy through a commercial supplier

b) Is the drug or device provided free of charge? ☐ Yes ☒ No
If yes, by whom?

4. **Preparation and Use:** Describe the method of preparation, storage, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.

NAC will be stored at the YNHH IDS pharmacy. Placebo will be placed in the same capsules as NAC, thus NAC and placebo will look and smell identical.

5. **Use of Placebo:** ☐ **Not applicable to this research project**
Provide a justification which addresses the following:
   a. Describe the safety and efficacy of other available therapies (if any).
   b. State the maximum total length of time a participant may receive placebo while on the study.
   c. Address the greatest potential harm that may come to a participant as a result of not receiving effective therapy (immediate or delayed onset.)
   d. Describe the procedures that are in place to safeguard participants receiving placebo.
      (a) Pharmacotherapy with SSRIs and cognitive behavioral therapy are both relatively safe and effective treatments for pediatric OCD (POTS 2004). We will recommend to all subjects considering enrollment in this trial that they engage in adequate trials (>3 months) of each of these interventions prior to enrolling in this trial. Assuming a child has significant residual OCD symptoms despite engaging in both these treatments, additional options include (1) antipsychotic augmentation, (2) switching SSRIs and (3) continuing on their current treatments.
         1. Antipsychotic Augmentation – Randomized, placebo-controlled studies in adults with OCD indicate that antipsychotic addition to ongoing SSRI monotherapy is a modestly effective treatment for refractory OCD. Estimates indicate that the Number needed to treat for this intervention is 5 with an outcome measure of treatment response. However, antipsychotic treatment is associated with significant side-effects including sedation, weight-gain, metabolic side effects such as diabetes and lipid abnormalities and the risk of extrapyramidal side effects such as tardive dyskinesia and akathisia. The risk of these side effects appears more pronounced in children than adults and no controlled studies for OCD have been conducted in these medications.
         2. For children who have tried only 1 SSRI an additional option is to switch to a different SSRI or SNRIs such as venlafaxine and clomipramine. There are no controlled studies assessing efficacy of medication switches in children with OCD. Data in adults suggest that if a patient has not responded to 1 SSRI the likelihood of responding to a different one is 25% and if they have not responded to 2 SSRIs, the likelihood of responding to a third is 10%.

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There is no significant evidence that the rate of response to switching to a serotonin norepinephrine reuptake inhibitor (SNRI) such as venlafaxine or clomipramine is any different. SSRIs are associated with side effects such as insomnia, sedation, nausea, diarrhea, sexual dysfunction, behavioral activation and suicidal ideation.

3. Continuing current therapies – current evidence suggests that the treatment response to SSRIs or CBT plateaus by 3 months after the initiation of treatment. The risk of continuing their current therapy varies based on the nature of that therapy, but does not contain the additional risks associated with NAC.

(b) 12 weeks.
Since the study medication is added to the children's current medications, the risk of symptoms worsening is not significantly greater in this clinical trial than it would be if the patient's medications were changed as part of standard clinical care. The only additional risks in this study are potential adverse effects of N-acetylcysteine or no response in the placebo group. We will monitor subjects carefully for these changes during the course of the study and discontinue the study and provide or refer subjects for appropriate treatment as necessary. Subjects assigned to placebo will have the opportunity to receive active NAC after the 12 weeks.

(c) If a child is discontinued from the study because of the worsening of symptoms, the child, if receiving active medication, will be referred for appropriate behavioral and pharmacological treatment, and if on placebo will be offered active medication in addition to the above therapy.

6. **Use of Controlled Substances:**
Will this research project involve the use of controlled substances in human subjects?
☐ Yes ☒ No See instructions to view controlled substance listings.

7. **Continuation of Drug Therapy After Study Closure** ☐ **Not applicable to this project**
Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended? ☒ Yes ☐ No
If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.
Subjects receiving placebo with receive NAC free of charge for the next 12 weeks of the protocol. They will continue clinical sessions as needed for the next 12 weeks. After receiving 12 weeks of NAC, they will be instructed on how to obtain NAC over-the-counter but encouraged to receive continued psychiatric care. We will make appropriate clinical referrals as necessary at the end of the trial. We will offer continued consultations to outside practitioners throughout the study period.

SECTION VII: HUMAN SUBJECTS

1. **Recruitment Procedures:** How will potential subjects be identified, contacted and recruited? Attach copies of any recruitment materials that will be used.

☒ Flyers	☐ Internet/Web Postings	☐ Radio
☐ Posters	☐ Mass E-mail Solicitation	☐ Telephone
☒ Letter	☐ Departmental/Center Website	☐ Television

☐ Medical Record Review ☐ Departmental/Center Research Boards ☐ Newspaper
☐ Departmental/Center Newsletters ☐ Web-Based Clinical Trial Registries
☐ Other (describe): ☒ Clinicaltrials.gov Registry (do not send materials to HIC)

1. a. **Assessment of Current Health Provider Relationship for HIPAA Consideration:**
Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐ Yes, all subjects
☒ Yes, some of the subjects
☐ No

If yes, describe the nature of this relationship.

We may recruit subjects who come to be seen at our clinic. Some children may be referred for psychopharmacology consult. Other subjects may come specifically because of interest in the study. No subjects will be taken off current medication or withdrawn from ongoing therapy in order to participate in the trial, unless the current medication is ineffective or causing unacceptable adverse effects. Families of children who are not interested in the study will be treated in the usual clinical manner.

2. **Subject Population** Provide a detailed description of the targeted involvement of human subjects for this research project.

In many cases subjects will be screened via telephone. The telephone screen will be used to inform the parent (primary caretaker) about the nature of the study, the duration of the study, number of visits, randomization, etc. The telephone screen will include collecting a brief history to exclude subjects that are unlikely to be eligible. People may not be eligible because of an ongoing medical problem (asthma or pregnancy), presence of an excluded psychiatric diagnosis (see exclusion criteria), or because they are unable to attend scheduled study visits. Interested subjects will be scheduled for a screening visit. The screening visit will occur over one visit. The overall purpose of the screening is to confirm that the subject meets all entry criteria. The first step in the screening visit will be to review the consent form, answer questions about the protocol and to obtain written informed consent. All procedures will be described to the subject in a developmentally appropriate manner.

2. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion? How will eligibility be determined, and by whom?

Subjects will be well-characterized and must meet selection criteria to be enrolled. The measures used in the baseline assessment will be used by the principal investigators to determine if subjects meet inclusion/exclusion criteria.

Inclusion Criteria:

1. Children aged 8-17 years.
2. Primary diagnosis of OCD.
3. Duration of OCD greater than 6 months.
4. Significant Current OCD symptoms: Current CY-BOCS score greater than or equal to 16.

Exclusion Criteria:

1. Comorbid bipolar disorder, psychotic disorder, substance use disorder, developmental disorder or mental retardation (IQ<70).
2. Recent change (less than 4 weeks) in medications that have potential effects on OCD severity (such as Selective Serotonin Reuptake Inhibitors, clomipramine, naltrexone, lithium, psychostimulants, anxiolytics, or antipsychotics). Medication change is defined

to include either dose changes or medication discontinuation.

3. Asthma requiring medication use within the last 3 months (case reports have linked intravenous NAC administration with asthma exacerbation)
4. Known hypersensitivity or previous anaphylactoid reaction to acetylcysteine or any components in its preparation.
5. Positive pregnancy test or drug screening test.
6. Previous use of N-acetylcysteine (dose greater than 600mg for more than 2 weeks).

3.a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☒ Yes ☐ No

3.b. If yes, will identifiable health information be collected during this screening process and retained by the research team? ☒ Yes ☐ No

4. **Subject Classifications: Check off all classifications of subjects that will be invited to enroll in the research project.** Will subjects, who may require additional safeguards or other considerations, be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☒ Children	☐ Healthy	☐ Fetal material, placenta, or dead fetus
☐ Non-English Speaking	☐ Prisoners	☐ Economically disadvantaged persons
☐ Decisionally Impaired	☐ Employees	☐ Pregnant women and/or fetuses
	☐ Students	☒ Females of childbearing potential

For children, we will obtain consent from their parent (legal guardian) before enrolling them in the study. We will also require childhood assent for participation. A simple quiz testing the understanding of the protocol and important elements of informed consent is in place at the end of the consent form.

For females of child bearing potential we will conduct a urine pregnancy test prior to enrollment in the study. If the pregnancy test is positive we will refer people to appropriate treatment and will exclude them from participation in the trial until completion of their pregnancy. For sexually active females, we will provide contraceptive counseling and refer them for contraceptive treatment if indicated. The acceptable methods of contraception will include oral birth control pills (OTCs), IUD, transdermal preparations, parenteral preparations, barrier contraceptive methods (i.e. condoms and diaphragm) and abstinence. Because full confidentiality regarding pregnancy cannot be entirely guaranteed, these testing requirements and the limited scope of confidentiality will be made known to all subjects during the consent procedure. In this manner, young women who would not be comfortable with pregnancy testing or sharing the results of such testing can “opt out” of the study at the time of the initial consent, without having to declare specific reasons.

Since subjects will also be screened for drugs, it would be advisable to explain that these results will also be kept confidential. However, if subjects exhibit any behaviors that could be an immediate danger to themselves or others and/or other serious medical conditions, subjects will be excluded, parents will be advised of these findings, and subjects will be referred for the appropriate evaluation. If subjects or parents are uncomfortable with the provisions surrounding drug testing, then, they may also opt out of participating.

a. Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

SECTION VIII: CONSENT/ ASSENT PROCEDURES

1. **Consent Personnel:** List all members of the research team who will be obtaining consent/assent.
   Michael H. Bloch, MD, MS, Angeli Landeros-Weisenberger MD, James F. Leckman, MD, Robert E. King, MD, Kaitlyn E. Panza, BA, Megan E. Smith, BA

2. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.
   - The research team (PI, his designee or research coordinator) will explain the study to the child and legal guardian.
   - Understanding of the study will be tested using a brief questionnaire (see consent and assent form) of the key elements of the study.
   - The research team will discuss the child's participation in the study with the patient's primary clinician and/or pediatrician. The clinician's opinion about the patient's participation and ability to provide informed consent will be documented.

3. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.
   Subjects will be minors (ages 8-17) and the consents will be obtained from the parent (guardians). We will also obtain assent from minors participating in our trial. The consent documents will be reviewed verbally with both parent and child. A brief questionnaire will be used to assess their basic understanding of our protocol – random assignment, need for regular visits, and the need for twice daily medication use. If for any reason, it becomes clear that either the parent or child can not comprehend trial design or procedures they will not be enrolled in this study.

4. **Documentation of Consent/Assent:** Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

Parental Consent Form, young child assent Form, adolescent assent form.

5. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. Translated copies of all consent materials must be submitted for approval prior to use.

This protocol will not involve Non-English speaking subjects. ☒

6. **Waiver of Consent:** Will you request either a waiver of consent, or a waiver of signed consent, for this study? If so, please address the following:
   ☒**This section is not applicable to this research project**
   Waiver of consent: (No consent form from subjects will be obtained.)
   a. Does the research pose greater than minimal risk to subjects? ☐ Yes ☐ No
   b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No

c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

Waiver of **signed** consent: (Verbal consent from subjects will be obtained.)
☒ **This section is not applicable to this research project**
a. Would the signed consent form be the only record linking the subject and the research? ☐ Yes ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects? ☐ Yes ☐ No
OR
c. Does the research pose greater than minimal risk? ☐ Yes ☐ No **AND**
d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

7. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:
☒ Compound Consent and Authorization form
☐ HIPAA Research Authorization Form

8. **Request for waiver of HIPAA authorization:** (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only)

Choose one: For entire study: _____ For recruitment purposes only: x___
i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data;
ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data;

i. **We are requesting a waiver of HIPAA authorization for recruitment purposes only. Subjects will be initially recruited through word of mouth, OCD advocacy organizations, physician referrals and internet ads. We will need to use PHI such as name, telephone number and email addresses to schedule initial screening interviews. It would be impractical to coordinate initial subject enrollment and recruitment without this data.**

ii. **Signed authorization is impractical because initial screening of patients recruited through advertisements or referral may occur over the telephone or email.**

By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

SECTION IX: PROTECTION OF RESEARCH SUBJECTS

1. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

The risks in this study include:

1) drug side effects of N-Acetylcysteine,
2) worsening of symptoms
3) length of research protocol and time required to complete study instruments
4) unanticipated side effects like nausea

Drug side effects

N-acetylcysteine (NAC) is an altered form of the amino acid cysteine, which is commonly found in food and synthesized by the body. N-acetylcysteine (NAC) is generally well tolerated and has been extensively used in the treatment of acetaminophen overdose/toxicity at high doses for many years. The dosage in acute acetaminophen overdose is a 140mg/kg loading dose followed by a maintenance dose of 70mg/kg administered every 4 hours for 17 consecutive doses. The long-term use of NAC has also been investigated in six-month to three-year studies examining the efficacy and tolerability of NAC (dosed between 600-1200mg per day) in the treatment of chronic obstructive pulmonary disease COPD (Pela, Calcagni et al. 1999; Grandjean, Berthet et al. 2000; Stey, Steurer et al. 2000; Kasielski and Nowak 2001; Poole and Black 2001; Chikina, Iagmurov et al. 2002; Decramer, Rutten-van Molken et al. 2005). A recent study by Decramer and colleagues in 2005 concluded that there were no adverse events thought to be drug related in their study examining the use of 600mg/day of NAC in over 500 patients with COPD. Additionally, Chikina and colleagues found that the most effective dose of NAC in the treatment of COPD was 1200mg/day (the study examined doses of NAC ranging from 600-2400mg/day). A meta-analysis examining the efficacy of NAC in COPD performed in 2000 revealed that NAC was well tolerated without significant adverse effects (Grandjean, Berthet et al. 2000). Although generally well-tolerated, the PDR indicates that adverse reactions reported with oral NAC include nausea, vomiting, diarrhea, headache (especially when used along with nitrates) and rashes. There are rare reports of renal stone formation. It is important to note that rare reports of bronchoconstriction have occurred with intravenous NAC (but no reports of bronchospasm related to oral use of NAC). Although there are no known contraindications to NAC use, individuals with asthma will be excluded from the study given the rare, but potential, adverse effect of bronchospasm.
We have treated a number of adult psychiatric patients with NAC at higher doses, up to 3000 mg/day, without side effects beyond mild nausea (Pittenger, Krystal et al. 2005; Lafleur, Pittenger et al. 2006).

Worsening of symptoms

Since N-Acetylcysteine is added to the patients' current medications, the risk of symptoms worsening in this study is probably not greater than it would be if the patient continued on their current medication. The only additional risks in this study are potential adverse effects of N-Acetylcysteine.

Ratings

Patients may find the battery of behavioral and movement ratings tedious.

Unanticipated side effects

NAC is commonly used in acetaminophen overdose as well as COPD. Although NAC has been shown to be effective and without adverse effects in adults with trichotillomania,

schizophrenia and bipolar disorder, the use of this medication in children with OCD might be associated with unforeseen risks, such as worsening of existing symptoms or emergence of new symptoms. All medications can be associated with allergic reactions. Any clinical trial involves risks and side effects that cannot be predicted. Subjects will be told of any important new information that might affect their decision to continue in the study. In addition, the HIC will be notified regularly of any new information about the safety of the study medication

2. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

   Subjects will be seen regularly during dose titration to monitor increases in the medication dose. Adverse effects will be systematically evaluated and documented with respect to severity and duration. Evaluation of adverse effects and dose are closely tied in so that the medication schedule is set up, such that decisions about dose increases occur at study visits. The treating clinician is free to delay an increase or reduce the dose at any time to manage a suspected medication-related adverse effect.

3. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.
   a. What is the investigator's assessment of the overall risk level for subjects participating in this study?
   b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?
   c. Data and Safety Monitoring Plan:

a) This trial is greater than minimal risk to the child, but presenting the prospect of direct benefit to the individual subjects.

b) This trial is greater than minimal risk to the child, but presenting the prospect of direct benefit to the individual subjects

c)

Data Management:

All data obtained during the course of the study will be stored both electronically and in hard copy. The study coordinator will be responsible for ensuring completion of all study forms and collection of all data materials. Study data will be entered into an electronic spreadsheet by dedicated data managers and/or study coordinators. Double data entry procedures will be used to ensure accuracy and completeness.

To protect the privacy of subjects, all information will be kept confidential and only members of investigative team, and the HIC will have access to the study data. All paper data will be maintained and secured in locked file cabinets. To further safeguard privacy, a numbering system will be used to assign a unique identifier to each subject. Each subject will have the same unique identifier for both paper and electronic spreadsheet. Only individuals with appropriate Human Research Subjects Protection training will be permitted to handle study subject data forms.

Safety Monitoring Plan:

Since this is a placebo-controlled, double-blind, study of children with OCD, we believe the risks involved in this study are greater than minimal risk to the child, but presenting the prospect of direct benefit to the individual subjects. However, assessment of adverse events, including grading of severity and attribution to research will be conducted at each visit. We will use the Pediatric Adverse Events Rating Scale (PAERS) to specifically track possible adverse events

throughout the trial (March, Karayal et al. 2007). Serious and unanticipated and related adverse events will be reported immediately to the HIC (using HIC form 6A), and any appropriate funding and regulatory agencies. Also, serious anticipated adverse events will be reported immediately to the HIC and others whenever their magnitude or frequency exceeds expectations. Dr. Bloch will evaluate the adverse event and determine whether the adverse event affects the Risk/Benefit ratio of the study and whether modifications to the protocol (at Risks to Subjects) or consent form (at Risks and Inconveniences) are required.

Personnel responsible for the safety review and its frequency.
Dr. Bloch will conduct a review of all adverse events at least quarterly and if any serious adverse events occur. He will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent forms are required. During the review process Dr. Bloch will evaluate whether the study should continue unchanged, require modification, continue or close enrollment.

Since this is a study of a FDA-approved medication in children with OCD, we believe the risks involved in this study are greater than minimal risk to the child, but presenting the prospect of direct benefit to the individual subjects. However, assessment of adverse events, including grading of severity and attribution to research, will be conducted at each visit indicated below.

1. Attribution of Adverse Events
Clearly: The adverse event is clearly related to the intervention
Likely: The adverse event is likely related to the intervention
Possibly: The adverse event may be related to the intervention
Unlikely: It is unlikely that the adverse event is related to the intervention
Not: The adverse event is clearly not related to the intervention

2. Plan for Grading Adverse Events
The FDA's definition of serious adverse events (21 CRF 312)
SAEs include any untoward medical occurrence that at any dose results in death or the immediate risk of death, hospitalization or the prolonging of an existing hospitalization, persistent or significant disability/incapacity or congenital anomaly/birth defect (NOH Guide-6/11/99)
Grades of Risk:
0 = No Adverse Event or within normal limits
1 = Non-Serious Adverse Event
2 = Serious Adverse Event

3. Plans for reporting serious and unanticipated and related adverse events, anticipated adverse events occurring at a greater frequency than expected, and other unanticipated problems involving risks to subjects or others to the HIC:
Serious and related unanticipated adverse events will be reported immediately to the HIC (using HIC form 6A), and any appropriate funding and regulatory agencies. Other unanticipated problems involving risks to subjects or others will also be reported to HIC.
Serious anticipated adverse events will be reported immediately to the HIC and others whenever their magnitude or frequency exceeds expectations. Dr. Bloch will evaluate the adverse event and determine whether the adverse event affects the Risk/Benefit ratio of the study and whether modifications to the protocol (at Risks to Subjects) or consent form (at Risks and Inconveniences) are required. For the current study, the following individuals, funding, and/or regulatory agencies will be notified:

a. All co-investigators

4. Plans for reviewing and reporting *non-serious anticipated and unanticipated* adverse events:
Dr. Bloch will conduct a review of all adverse events at least quarterly. He will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent forms are required.

4. **Confidentiality & Security of Data:**

a. What protected health information about subjects will be collected and used for the research?

b. How will the research data be collected, recorded and stored?

c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☐ Portable Hard Drive ☐ Secured Server ☒ Laptop Computer ☒ Desktop Computer ☐ Other

d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during the subject participation in the study?

e. What mechanisms are in place to ensure the proper use and continued protection of these data after the subject participation in the study has ceased?

f. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

g. Who will have access to the protected health information? (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, QUACS, SSC, etc.)

h. Which external or internal individuals or agencies (such as the study sponsor, FDA, QUACS, SSC, etc.) will have access to the study data?

i. If appropriate, has a Certificate of Confidentiality been obtained?

j Are there any mandatory reporting requirements? (Incidents of child abuse, elderly abuse, communicable diseases, etc.)

(a) Private identifiable information will be collected but will be kept confidential and will not be divulged in any publication emanating from this work

(b) Clinical data, outcomes of diagnostic instruments, and research data will be collected by the principal investigator and other study personnel and stored in a locked file cabinet in a locked office. Data will be entered into a database on a password-protected computer in a locked office, by study personnel.

(c) Above

(d) All data will be coded and stored in locked cabinets/password protected computer in an office that is locked. Information that will breach subject confidentiality will not be shared. Rather, data will only be released upon written consent of the subject and will be available for review by the Yale human Investigation Committee.

(e) The consent form will ask families to provide consent to contact them in the future. This request will make it clear that participation in the study is not contingent on granting this permission. Furthermore, granting permission to be re-contacted does not obligate the family to participate in any future project. Published reports will contain only aggregate data and will be free of personal identifiers.

(f) We will hold paper files for seven years at which point they will be destroyed. As noted above, archived computer files will not have any identifying information.

(g) Principal investigator, co-investigator and study personnel.

(h) The International Obsessive-Compulsive Disorder Foundation is a potential sponsor of this project and could have access to trial data if they come to Yale to monitor the conduct of this research study.
(i) We will not preserve drug screening data after completion of tests so we will not apply for a certificate of confidentiality.
(j) Yes. Evidence of child abuse or situations in which the subject is deemed a danger to self or others will be reported.

5. **Potential Benefits:** Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

Children may benefit from the thorough medical and psychiatric evaluations that they will receive while participating in the study. During the study, subjects will also receive a higher level of evaluation and care than routine treatment. Additionally, subjects may benefit from the study medication.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

1) Continuing patient's current medications or therapy, which might include various SSRIs or clomipramine) or cognitive behavioral therapy. Both these interventions have demonstrated efficacy for the treatment of pediatric OCD. All subjects will be recommended to engage in adequate trials of both these interventions before enrolling in the trial.
2) Antipsychotics in addition to SSRIs have shown some benefit for the treatment of refractory OCD in adults. These medications are associated with a significantly greater side effect burden than NAC. Families will be made aware of this additional treatment option prior to enrolling in this study.
3) Since N-Acetylcystiene is FDA approved for use to reduce the extent of liver injury after acetaminophen overdose, the patient's doctor might feel comfortable prescribing it off label to the patient.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects and the conditions for receiving this compensation.
Subjects will be paid a total of $150 for participation in the study -- $50 screening assessment, $25 for each of the 4 follow-up visits. .

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.
Families will not be charged for the study medications, clinical assessments, services or laboratory tests directly related to the study. As noted above, some subjects may be seen for a clinical consultation prior to study entry. This clinical consultation will be charged as part of standard of care in the usual manner.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.

a. Will medical treatment be available if research-related injury occurs?
b. Where and from whom may treatment be obtained?
c. Are there any limits to the treatment being provided?
d. Who will pay for this treatment?
e. How will the medical treatment be accessed by subjects?

(a) Yes

(b) Initial assessment and appropriate referral will be carried out by the research team. The PI (Michael H. Bloch, MD) will conduct assessment under the supervision of Dr. King and Dr. Pittenger. Whether these events were considered "related to the study treatment" or not, our research team will participate in the assessment and appropriate disposition of the case. The disposition has taken many forms: in some cases, we assume ongoing clinical care of the subject; in other cases, we secure appropriate referrals and are no longer involved in the patient's care; other cases may involve a combined approach in which we provide care in collaboration with appropriate specialists. In all cases, the disposition is guided by the family's preference and clinical judgment regarding the subject's best interest. Every reasonable effort will be made to involve the subject's primary care provider.

(c) Our intervention will focus on assessment and securing an appropriate referral in collaboration with the family and the primary care provider.

(d) We will provide our assessment and referral services without charge. Ongoing care will be paid by the family or family's insurance carrier.

(e) As noted in 4b, the occurrence of an adverse event requiring care outside the confines of the study will be initially assessed by the research team. Referrals to the family's primary care provider or other specialists will be made in accordance with the nature of the subject's problem.

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