A Multidisciplinary Approach to the Treatment of Encopresis in Children with Autism Spectrum Disorders

Department of Defense Study

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NCT Number: NCT03197922

Protocol Version 4.3
Protocol date: August 24, 2021

History of Protocol Changes

Version 4.3 08/24/2021

- **Added REDCap as a data collection tool for collecting consent signature and parent measures.**

Version 4.2 06/15/2020

- **Added in the ADI-R and CARS-2 assessments as additional ASD diagnostic tools**
- **Added in the option to do the medical assessment through telehealth, specifically zoom**

Version 4.1 03/18/2020

- **Added language to include that TAU and MIE appointments can be through Telehealth**
- **Corrected total enrollment number to 138 instead of 112 because 112 did not include the participants that were previously enrolled into the MIE 1 week group**

Version 4.0 10/15/2019

- **Removed MIE 1 week group**
- **Corrected visit window and continence language**

Version 3.9 05/30/2019

- **Corrected title of protocol**
- **Changed IRB notification of "would" to "may" for cases of problem behavior.**
- **Removed language about participants being enrolled in IRB #53959.**
- **Included information on holds/restraining for participants engaging in problem behavior**

Version 3.8 01/24/2019

- **We changed the definition of "urine continent" under our inclusion criteria. It will now be "Over half of the voids are continent when the child is with the parent and when the child is on a typical toileting routine.**
- **We removed number 6 under inclusion criteria because in our last amendment we said subject would no longer be enrolled in our IRB# 53959**
- **We removed the section on the top of page 22 that says, "**Also, subjects will be enrolled in IRB 53959 (MAC), which permits and facilitates the collection of their data. If the subject does not agree to be in IRB 53959, they will be excluded"
- **Version 3.7 06/18/2018**
- **Medical screening can be conducted by a nurse practitioner with consultation from a pediatric gastroenterologist**
- **Subjects will no longer be enrolled in our IRB #53959**

Version 3.6

- In Recruitment section, revised protocol to state that we will now be using the Oral Consent and HIPAA Authorization Script and Information Sheet for Research Study Screening instead of the Screening Protocol – IRB# 00057294

Version 3.5, drafted 01/08/2018

- Randomization to group assignment will now take place after Characterization and Medical Screening are completed (after all eligibility criteria have been met)
- Visit windows for Week 4 (midpoint), Week 8 (endpoint), and Week 28 (follow-up) will be counted from Baseline Visit (the day baseline measures are collected)
- Added concomitant medication log to table of measures, baseline, midpoint, endpoint and follow up
- In the Screening Process section, edited protocol to state that we will now be using the Oral Consent and HIPAA Authorization Script and Information Sheet For Research Study Screening instead of the Screening Protocol – IRB #00057294

Version 3.4, drafted 11/27/2017

- Added caregiver log of frequency of child's continent and incontinent bowel movements to the time period between the phone screen and characterization appointment
- Added the Mullen Scales of Early Learning (MSEL) as a possible characterization measure
- Added research coordinators to the list of personnel who will administer characterization measures
- Renamed screening as Characterization and Medical Evaluation to differentiate it from Phone Screen.
- Stipulated that the Characterization and Medical Evaluation can take place across 1 or 2 days.
- Corrected an error in the dosing of the suppository.
- Increased the visit windows for the Endpoint and Follow up
- Added Midpoint to the schedule of measures
- Added statement that the BPI will be reviewed by a doctoral level member of the study team at Characterization to determine participants do not meet exclusion criterion for interfering problem behavior.
- Clarified that the sequence of characterization and medical screening can vary
- Clarified that the TAU appointment can last up to 2 hours, but does not have to last exactly 2 hours
- Added a section describing the informed consent process
- Added the Verbal Consent form to the Screening process

Version 3.3, drafted 09/25/2017

- Updated the definition of continence

Version 3.2, drafted 09/20/2017

- Added caregiver log of frequency of child's continent and incontinent bowel movements to the time period between the phone screen and characterization appointment
- Added the Mullen Scales of Early Learning (MSEL) as a possible characterization measure
- Added research coordinators to the list of personnel who will administer characterization measures
- Updated specific aims
- Added Analytic plan
- Updated reporting method of AE's and SAE's
- Added dosing table (Table 3.0)

Version 3.1, drafted 09/19/2017

- Clarified that the visit to the gastroenterologist will be uploaded to the medical record
- Visit windows for Week 8 and Week 28 will be counted from the start of treatment and not from Baseline. This is because the Baseline window ranges from 2-3 weeks before treatment starts
- Modified Week 8 visit window to be 6 weeks +/- 3 days from the start of treatment and Week 28 visit window to be 26 weeks +/- 5 days from the start of treatment
- Treatment (either MIE or TAU) must occur 12-21 days after Baseline. During this time families must collect 7 days of home toileting data (data sheets will be provided to families). These 7 days do not need to be consecutive.
- Added description of Case Panel reviews when exceptions to Inclusion/Exclusion criteria occur
- Changed CGSQ to CGSQ-Short Form (CGSQ-SF)
- Added CGSQ-SF to Week 8

Version 3.0, drafted 07/06/2017

- Added Aberrant Behavior Checklist
- Added King's Stool Chart
- Updated Inclusion/Exclusion criteria to clarify that all medical conditions will be reviewed by study team to determine eligibility
- Updated Inclusion/Exclusion criteria to add that we will only enroll subjects with one or fewer episodes of incontinent urination each day
- Added recruitment projection table

Version 2.0, drafted 05/02/2017

- Added description of intervention methods
- Added schedule of measures

- Added description of Adverse Event review and Data Safety Monitoring Plan
- Added visit windows for all assessment visits
- Described the minimum number of MIE appointments required for both 1- and 2-week MIE treatment groups
- Described the different amount of study medication subjects in the MIE treatment groups will be sent home with and how this determination is made

Version 1.0, drafted 03/28/2017
Original protocol submission

Background & Significance

Toilet training one's child is a nearly universal challenge for parents, but is a particularly distressing ordeal for parents of individuals with autism spectrum disorder (ASD). Whereas typically developing children generally stop having daytime toileting accidents (i.e., they achieve continence) by 2-4 years of age (Blum, Taubman, & Meneth, 2003; Butler, 1997; Heron, Joinson, Croudace, & von Gontard, 2008; Schum et al., 2005), most individuals with ASD are either delayed in their acquisition of toileting skills, or never achieve continence. Furthermore, toileting concerns are a significant contributor to the increased stress experienced by caregivers of those with ASD (Macias, Roberts, Saylor, & Fussell, 2006). Besides dramatically increasing their burden of care, not being fully toilet trained negatively impacts the individual with ASD's hygiene, self-confidence, physical comfort, and independence while also causing social stigma (Cicero & Pfadt, 2002; Sells-Love, Rinaldi, & McLaughlin, 2002). Incontinence can also have serious collateral consequences, such as limiting exposure to important life experiences. Furthermore, without effective treatment these problems generally persist into adulthood (Benninga, Voskuijl, & Taminiau, 2004).

Only a small number of studies report successful treatment of encopresis in individuals with ASD. In an example of one of the few such studies, Smith (1996) describes successful treatment of encopresis in 5 teenage boys. Treatment included frequent checks for incontinent bowel movements, with reinforcement for staying clean. Participants were also encouraged to sit on the toilet for at least 10 min following meals, in the hope that a continent bowel movement would occur that could be positively reinforced. Although this and a few other studies report successful treatment of encopresis, they have all been case studies with a small number of participants (Lyon, 1984; Scott, 1977), with the results for the five participants by Smith representing one of the largest samples to date. These existing studies have also employed weak experimental designs (Lancioni & Markus, 1999). Most also fail to provide information about important participant characteristics such as cognitive and receptive language skills (Cicero & Pfadt, 2002; Post & Kirkpatrick, 2004). Many also fail to provide basic details about training procedures and outcome measures, or included participants with and without disabilities (Lancioni, O'Reilly, & Basili, 2001). Perhaps most limiting, the majority of published examples of the successful treatment of encopresis have required

implementation over long periods. For example, the average duration of treatment in the study by Smith was 98 weeks. The combined effect of these limitations is that encopresis generally remains untreated in most individuals with ASD.

One reason why strictly behavioral treatments of encopresis have shown only limited success may be due to the fact that it often has a medical etiology. That is, long-standing constipation is the cause of encopresis in the majority of children who exhibit it (Chase, Homsy, Siggaard, Sit, & Bower, 2004; Mason, Tobias, Lutkenhoff, Stoops, & Ferguson, 2004; Koivusalo, Pakarinsen, & Rintala, 2006). Children with ASD are 3.8 times more likely to have constipation than typically developing children (McElhanon, McCracken, Karpen, & Sharp, in press). Constipation causes encopresis by creating a cycle of withholding bowel movements: constipation causes painful bowel movements, which triggers further withholding behavior (Fishman, Rappaport, Cousineau, & Nurko, 2002), exacerbating constipation. Withholding is the voluntary contraction of the external sphincter to avoid a bowel movement. Subsequently, the colon accommodates the fecal mass and the urge to defecate is delayed. The postponed bowel movement allows more water to be absorbed from the colon and creates a harder stool. Over time the colon adapts by dilating, which leads to larger fecal masses in the rectum. Thus, the passage of larger and harder (i.e., painful) stools further increases an individual's withholding behavior. Of note, 63% of children with encopresis have a history of painful defecation beginning before 36 months of age (Lewis & Rudolph, 1997). Over time, the rectum and colon become so dilated that the individual loses sensation. With no urge to defecate, an individual is even more likely to have stool accumulate in the rectum and is also unable to control bowel movements. Looser stool may leak around hard stool leading to an unintended leakage and sometimes large evacuation of stool occurs without the individual realizing it.

Although purely medical approaches can successfully treat constipation in individuals with ASD, they have not shown long term success with encopresis. That is, medical approaches can treat a single episode of constipation, but without acquiring toileting skills, the individual is likely to become constipated again, repeating the cycle (29). Conversely, purely behavioral strategies have not been shown to be effective at treating encopresis in individuals with ASD, even when they are not experiencing constipation (see above). One reason for this lack of success may have to do with the fact that it is often difficult to predict the timing of a bowel movement so that caregivers can ensure the individual is sitting on the toilet when one takes place and then reinforce continence.

Thus, it is clear that a multidisciplinary approach incorporating both medical and behavioral approaches is necessary in the treatment of encopresis in individuals with ASD. Medical approaches can resolve episodes of constipation prior to treatment and provide a regimen that increases the predictability of a bowel movement, allowing clinicians to prompt the individual to sit on the toilet beforehand. Once a continent bowel movement occurs it is then amenable to behavioral strategies such as positive

reinforcement. A few promising interventions to date have attempted such a combined behavioral/medical approach. For example, Piazza, Fisher, Chinn, and Bowman (1991) reported successful treatment of encopresis in two participants using hourly trips to the toilet, positive reinforcement, and laxatives. Despite promising results, such studies are few in number and include only a few participants each. Furthermore, no studies to date have incorporated good experimental control. That is, the multiple behavioral and medical procedures were introduced and/or removed in a non-systematic fashion, making it impossible to determine which elements contributed to the results.

In response to the absence of an effective treatment for encopresis in this population, our clinical team developed a novel Multidisciplinary Intervention for Encopresis (MIE) in children with ASD. Within MIE, medical professionals resolve any constipation and oversee a regimen of over the counter medications that increase the predictability of a bowel movement. Our medical regimen differs from those employed in previous studies. Prior studies have used laxatives, enemas, or a combination of these. However, suppositories are more appropriate for this purpose because bowel movements generally occur shortly after they are administered. The medication regimen employed in this study includes the use of a glycerin suppository. These work by attracting water into the rectum and gently promoting a bowel movement (Fleet Company Incorporated). If a glycerin suppository is insufficient to elicit a bowel movement alone, then a bisacodyl suppository is administered, which directly stimulates sensory nerves, amplifies peristaltic contractions, and moves feces out within 15 minutes to an hour (Physicians' Desk Reference Network, LLC). When a continent bowel movement occurs, potent positive reinforcers that have been identified previously are administered. Previous research on treating encopresis and enuresis has suggested that such reinforcement is often sufficient to increase the child's motivation to have continent bowel movements. As independent continent bowel movements begin to occur, the need for the medical regimen diminishes, and is gradually faded out entirely. The goal of MIE is to establish sufficient continence during clinic-based treatment that the intervention can be turned over to caregivers following training and further increase independent continence. Significantly, treatment in the clinical setting lasts for no more than 10 days, with many patients achieving initial continence in as little as 5 days.

It is important to note that although the use of rectal suppositories may seem invasive, a majority of the patients receiving MIE to date have been receiving regular administration of suppositories or more invasive procedures (i.e., enemas) prior to starting MIE to manage constipation. Furthermore, long term use of these medical procedures is likely to be required without an effective treatment. For example, we treated one young man who required regular sedation (i.e., approximately every 3 weeks) in order to receive an enema because he almost never had a bowel movement and became combative when his caregivers or gastroenterologist attempted to remove impacted stool using an enema. This cycle of highly invasive procedures had become so chronic that his doctor was considering inserting a stoma and attached colostomy bag.

Instead, this patient successfully completed MIE and is now consistently independent in his continence. Thus, for patients in need of MIE, like this young man, the use of suppositories is either not new and/or is less intrusive than the alternatives. Finally, caregivers of participants in a pilot study of MIE did not appear to be concerned about the use of suppositories, as on average they rated MIE as 6.9 out of a possible 7 on program acceptability.

Further strengthening our project is the fact that our interdisciplinary research group has implemented this treatment protocol clinically with good success. To date, we have conducted MIE in the Toileting Services Program of the Marcus Autism Center with 34 patients (31 males, 3 females), ranging in age from 3 to 14 years (M = 8.37 years). To date we have been able to collect follow-up data on maintenance of continence for 15 of these patients approximately 4 months after discharge. Using the definition of continence appearing in the literature of fewer than 3 bowel movement accidents per week (Blum et al., 2004), 93% of patients who had completed MIE maintained continence at follow-up. Furthermore, for 67% of these patients' caregivers reported that their child had no bowel movement accidents following discharge from MIE.

Specific Aims

Primary Aims

1) Evaluate the efficacy of a two-week, multidisciplinary intervention for encopresis (MIE-2) in children with ASD compared to controls receiving Treatment as Usual (TAU). We predict, based on parent report, that a significantly greater proportion of subjects in the MIE-2 group will achieve continence at endpoint (Week 8) than children in TAU.

2) Evaluate whether the MIE-2 group will have a significantly higher proportion of children rated *Much Improved* or *Very Much Improved* on the Improvement item of the Clinical Global Impression than children in TAU as rated by an Independent Evaluator blind to treatment assignment at Week 8.

3) Evaluate whether parents of children in MIE-2 will report greater reduction from baseline in parental stress and strain than parents of children in TAU at endpoint (Week 8) as measured on the Parenting Stress Index and the Caregiver Strain Questionnaire.

Procedures

This is a 28-week, randomized clinical trial of 138 (updated from 150) children, ages 5 to 12 years, 11 months with ASD and encopresis. Subjects will be randomized in a 1:1 ratio to receive either two weeks of MIE or one week of Treatment as Usual (TAU). See Figure 1 for an outline of study procedures described below.

As shown in the Figure, Week 8 is an important nodal point in the study. At Week 8, participants will be classified as having achieved continence or not. This classification at Week 8 is the primary outcome for the study.

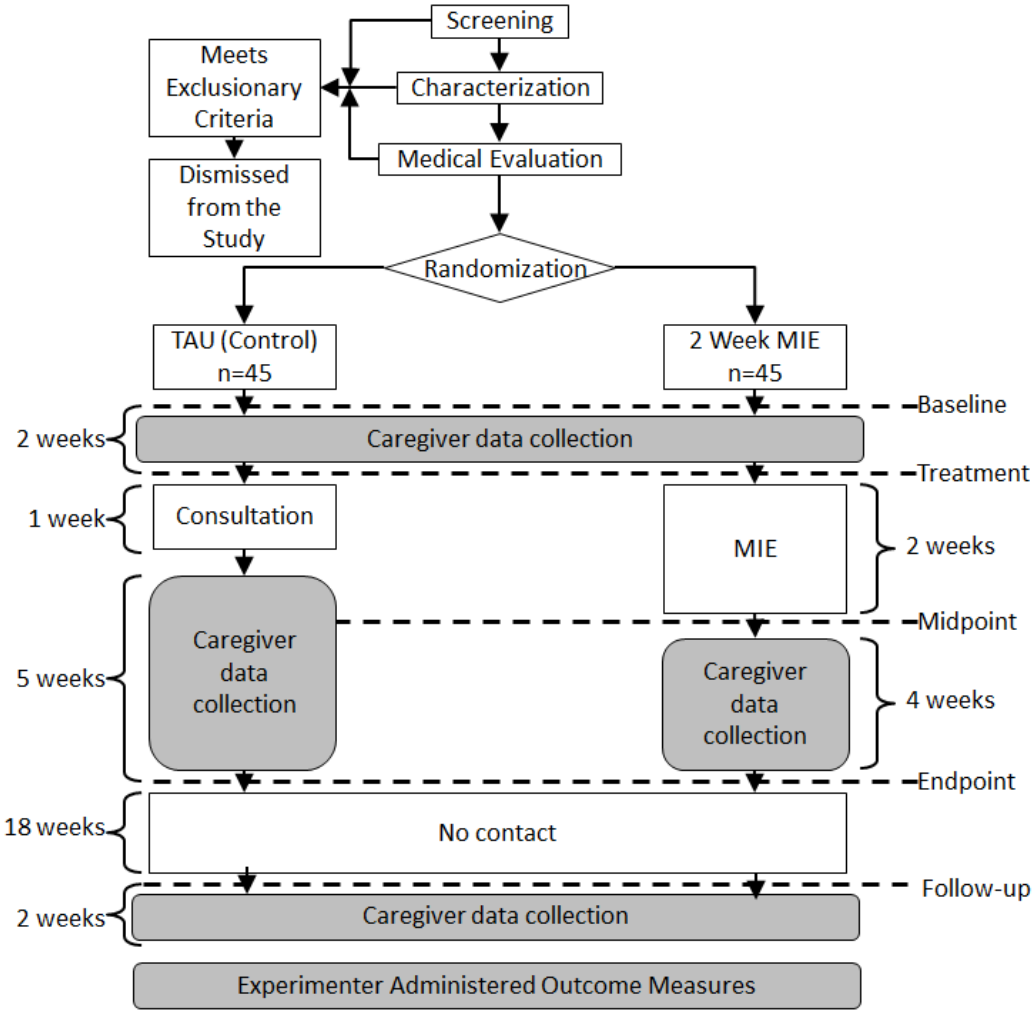

Figure 1

Screening: Prior to enrollment all potential participants will be evaluated for study eligibility through an initial phone screen. At the beginning of this screening, we will provide the family with a short study synopsis. We will then complete the Oral Consent and HIPAA Authorization Script and Information Sheet for Research Study Screening. This is a verbal consent form that gives us permission to collect and store protected health information over the phone. This form will be read to the families to ensure they understand the information we are collecting and their rights as a research subject. This screening will consist of gathering information on the participants' age, parent reported diagnosis, and problem behavior. Participants will be excluded if their caregiver does not report that the child meets the age or diagnostic criteria. If the caregiver indicates that the child engages in problem behavior, additional information

will be gathered to determine if problem behavior is likely to interfere with the treatment protocol. If problem behavior is deemed likely to interfere they will be excluded from participation. Caregivers will also be asked to keep a log of the frequency of their child's continent and incontinent bowel movements from the day of the phone screen until the characterization appointment to further confirm study eligibility.

Characterization, the Medical Assessment, and collection of Baseline Measures will take place across either 1 or 2 days, depending on participant and clinician availability, as well as the ability of the participant to tolerate lengthy assessments. Although the medical screening may precede characterization if scheduling requires, characterization will take place first whenever possible because participants are thought to be more likely to meet diagnostic exclusionary criteria than medical exclusionary criteria.

Consenting: A member of the research team will obtain informed consent from the caregiver(s) of each participant prior to completing any study procedures. We will not obtain assent from participants because it is anticipated that most will not possess the cognitive capacity to give assent and because refusal to comply with toileting routines is the condition that is being targeted for intervention. At this meeting caregivers will be asked to keep concomitant medications stable and to notify us if this is not the case during the study. Caregivers of participants will be provided a handout that addresses frequently asked questions about the use of suppositories.

Characterization: Once a participant has completed the phone screening a research coordinator will schedule an appointment for characterization. This appointment will include completion of the Autism Diagnostic Observation Schedule (ADOS), Autism Diagnostic Interview – Revised (ADI-R), and/or Childhood Autism Rating Scale – Second Edition (CARS-2), Vineland Adaptive Behavior Scales-3, Child Symptom Inventory, Demographics (i.e., Global Unique Identifier [GUID], The Behavior Problem Inventory (BPI) and either The Differential Ability Scales (DAS-II) or The Mullen Scales of Early Learning (MSEL) (depending on participant age; See Table 1 – Schedule of Measures). Characterization measures will be administered by doctoral level psychologists, post-doctoral fellows working under the supervision of a licensed psychologist, or research coordinators. A doctoral level member of the study team will review the BPI to determine whether participants meet the exclusionary criterion based on the presence of problem behavior that is likely to interfere with treatment.

Medical Assessment: Following the characterization appointment, all participants with a confirmed ASD diagnosis will undergo Medical Screening by a licensed and board-certified pediatric gastroenterologist or a nurse practitioner (NP) working in consultation with a board-certified pediatric gastroenterologist, to ensure that the participant meets medical inclusion criteria and to provide medical clearance for use of glycerin suppositories and bisacodyl suppositories. In addition, during this appointment participants will be evaluated to determine constipation status and begin treatment for

constipation per established guidelines (Furata et al., 2012), if necessary. During the medical screening, the physician and/or NP will confirm that the participant is eligible (i.e. does not meet medical exclusions as above). Participants randomized to the Treatment as Usual Group (TAU) and who are also constipated will continue to receive treatment for constipation throughout the clinical trial and follow-up. Participants randomly assigned to the MIE treatment group will also be evaluated for constipation and receive medical treatment during baseline. The medical assessment will take place either in the building at Marcus or via telehealth, specifically zoom.

Group Assignment: Participants will be randomly assigned to one of the two groups after they have it has been verified that they meet all of the eligibility criteria. Randomization to 2-week MIE or TAU will be according to a 1:1 ratio using permuted blocks stratification on constipation status. The permuted blocks will be constructed and managed by the unblinded statistician. She will receive an email form from the coordinator indicating that the participant meets all inclusion criteria and does not meet any exclusion criteria and the participant's constipation status (constipated/not constipated). This statistician will assign the subject to 2-week MIE or TAU according to the permuted block. We define constipated using the modified Rome III criteria appearing above. All other participants will be considered not constipated. Caregivers of participants randomly assigned to the MIE condition (i.e., 2 week) will be provided a handout that addresses frequently asked questions about the use of suppositories.

In the event a participant is unable to attend MIE or TAU visit(s) in the clinic after being enrolled into their assigned group, the clinician and therapists have the option to administer the intervention or TAU consultation via telehealth with the participant (e.g., WebEx, Zoom). In order to utilize telehealth, a scenario must arise that prevents the participant from being able to complete the MIE treatment or TAU consultation in the clinic. If such a scenario arises, on a case-by-case basis, then the therapist and clinician may administer via telehealth, but should return to the clinic as soon as possible to continue. Additionally, there will be one extra day added to the MIE 2-week treatment totaling 11 days instead of 10. The extra day is added to the beginning of treatment so the clinician can first explain the intervention they will be doing with the caregiver.

Baseline Phase (Weeks 1-2): All participants' caregivers, regardless of group assignment will implement any medical recommendations for constipation throughout a Baseline Phase. In addition, all caregivers will collect data on their child's bowel movements during Baseline. It is anticipated that this phase will last for 14 days, but due to scheduling issues it may last for 12 to 21 days. Data collection will include frequency of continent and incontinent bowel movements and whether any medication (i.e., a suppository) was used prior to the bowel movement on data sheets provided by the research team. Caregivers will be asked to enter data from the datasheets electronically directly into our project database via a unique and secure login provided during the characterization visit. Caregivers who do not enter data for a given day will receive a reminder email the next day. A research coordinator will also call caregivers who are missing data on a weekly basis to see if they entered it on the datasheet but did

not enter it electronically. In cases in which the family does not have access to the internet, the data will be collected over the phone. Caregivers will be asked to bring the data sheets to their first visit in the clinic.

Baseline Visit: Baseline data will be collected on the first day of MIE or TAU, before the appointment occurs. A member of the research team will meet with caregivers to complete the remaining baseline measures. The following measures will be completed: Parent Target Problem (PTP), Parenting Stress Index-Short Form (PSI-SF), Aberrant Behavior Checklist (ABC) Clinician Global Impression-Severity (CGI-S), Caregiver Strain Questionnaire-Short Form (CGSQ-SF), Adverse Event, Safety Review, Concomitant Medication Log .

Treatment (Weeks 3-4): Participants randomized to the TAU group will continue to receive outpatient medical treatment of encopresis according to best practice guidelines by the pediatric gastroenterologist. In addition, participants in the TAU group will receive an individual appointment lasting up to 2-hours in clinic or via telehealth with a doctoral level clinician with extensive experience in behavioral treatments for encopresis. This outpatient appointment will include didactic presentation of a PowerPoint presentation and consultation regarding treatment of encopresis. During the appointment, the clinician will review strategies to increase continence. Specifically, the clinician will provide parent education on the following topics: how to collect and evaluate data on their child's bowel movements, how to establish and use a sit schedule, identifying behaviors that are precursors to bowel movements and how to use them to increase the probability of a bowel movement being continent, consequences for incontinence, and reinforcement for continence. These recommendations will be individualized based upon data collected during baseline. In addition, participants in the TAU group will continue to implement any medical treatment for constipation as prescribed.

Following the baseline phase, participants randomly assigned to the MIE group (i.e. 2 weeks) will begin treatment in the form of daily clinic visits or via telehealth (≤3 hrs./appointment) for 2 weeks (5 days/week). In addition, these participants will discontinue the use of medication prescribed for the treatment of constipation, other than the suppositories used in the MIE treatment. [RATIONALE: it is expected that participants will have daily bowel movements during the 2 weeks of MIE, and laxatives or other medicines may interfere with participants' ability to recognize and act upon the need to have a bowel movement (i.e., "pushing")]. During treatment all participants receiving MIE will be monitored for constipation and the pediatric gastroenterologist will be contacted to determine if additional medications are needed if more than three days pass without a bowel movement. At the conclusion of the clinic-based phase of treatment caregivers will be trained to implement MIE with ≥90% fidelity to the protocol, and told to continue to use the procedures upon discharge.

Assessments during the randomized trial Assessment of therapeutic response and

adverse events will be conducted at Midpoint (Week 4) and Endpoint (Week 8). Outcome measures, including the Parent-nominated Target Problem (PTP), will be conducted by separate independent evaluators (IE) each of whom are blind to treatment assignment. Additional measures collected at the Endpoint visit include the Parent Target Problem, Parent Stress Index, Caregiver Strain Questionnaire, and Treatment Acceptability Rating Form- Revised, Aberrant Behavior Checklist, Clinician Global Impression-Improvement, Clinician Global Impression-Severity, Concomitant Medication Log, Safety Review, and Adverse Events(see Table 1).

Follow-up (Weeks 26-28): At Week 17 caregivers will be reminded that we will evaluate their child's progress during Weeks 27 and 28. Data collection during this follow-up period replicates the procedures during baseline and treatment (caregiver recording of continent/incontinent bowel movements, the use of medication, and self-initiation). In addition, all measures collected at the endpoint visit in the randomized trial will be repeated at the conclusion of Follow-up (Week 28), including the Parent Target Problem, Parent Stress Index, Caregiver Strain Questionnaire, and Treatment Acceptability Rating Form- Revised, Aberrant Behavior Checklist, Clinician Global Impression-Improvement, Clinician Global Impression-Severity, Concomitant Medication Log, Safety Review, and Adverse Events.

Schedule of Measures

Table 1.0 – Schedule of Measures

	Characterization & Medical Assessment	Baseline Measures	Treatment (MIE)	Week 4 (Midpoint)	Week 8 (Endpoint)	Week 28 (Follow Up)	Staff	Time (m)
ABC		X		X	X	X	IE	15
ADOS, ADI, and/or CARS-2	X						CAC	60
BPI	X						RC	15
CGI-I				X	X	X	IE	5
CGI-S		X		X	X	X	IE	5
CGSQ-SF		X			X	X	CG	7
Constipation Status	X						GI	30
MPHR	X						RC	10
CSI	X						RC	15
DAS or Mullen	X						CAC	45
Demographics	X						CG	10
PSI		X			X	X	CG	5
PTP		X		X	X	X	IE	20
TARF-R					X	X	IE	15
Concomitant Medication Log		X		X	X	X	IE	10
Adverse Event		X		X	X	X	IE	5
Safety Review		X		X	X	X	IE	10
Vineland (Survey)	X						RC	30
Therapist Measures								
Continence			Daily	X			TH	-

			during MIE					
Independence			Daily during MIE	X			TH	-

Table 2.0 - Caregiver Home Data Collection Schedule

Study Phase	Baseline	Treatment	No Contact	Follow Up
Study Phase duration	**2-3 Weeks**	**8 Weeks**	**18 Weeks**	**2 Weeks**
Measures				
Continence	Daily	Daily	-	Daily
Independence	Daily	Daily	-	Daily
King's Stool Chart	Daily	Daily	-	Daily

Reminder Calls: During the 18 Week Home Implementation Phase, the study team will make monthly, scripted phone calls to participants. These phone calls will serve to remind the parents to continue to implement the intervention procedures they were taught and to confirm that they have an adequate supply of study medication. These calls will be scripted and parents will not be given any additional insight or clinical guidance. If necessary, parents will be reminded that they are participating in a research study and that the goal is to determine the intervention's effectiveness up to their Week 28 Follow Up visit. Parents will also be reminded that they will receive clinical guidance after completion of their Week 28 visit. However, the study team may intervene clinically and terminate study participation if they feel the child is in need of immediate emergency medical treatment.

Visit Windows

The visit window between Characterization/Medical Assessment and Baseline/MIE Treatment or the TAU consultation visits is 12 – 21 days. MIE Treatment or the TAU consultation visit must occur after the Week 2 Baseline. During this time, parents must collect a minimum of 7 days of toileting home data. These days do not need be consecutive.

The Week 4 Midpoint visit will occur 7-21 days after the Week 2 Baseline Visit (2 weeks +/- 7 days). The Week 8 Endpoint visit will occur 35-49 days after the Week 2 Baseline Visit (6 weeks +/- 7 days).Week 28 Follow Up will occur 175-189 days after the Week 2 Baseline Visit (26 weeks +/- 7 days).

Study Measures

Characterization Measures:

Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000) The ADOS is an

investigator-based procedure that places the child in naturalistic social situations demanding specific social and communication reactions. The ADOS provides a sample of the child's behavior in a naturalistic setting. Behaviors are coded in the areas of social communication, social relatedness, play and imagination, and repetitive behaviors. The ADOS contributes to the DSM 5 diagnosis of ASD.
Autism Diagnostic Interview-Revised (ADI-R) (Rutter, LeCouteur, & Lord, 2003). The ADI-R is a structured interview that is used to diagnose autism. The interview can be administered to a caregiver and is composed of 93 items. The instrument includes the three functional domains related to ASD: Language and Communication, Reciprocal Social Interactions, and Restricted, Repetitive, and Stereotyped Behaviors and Interests.

Childhood Autism Rating Scale-Second Edition (CARS-2) :The CARS-2 (Schopler, Van Bourgondien, Wellman, & Love (2010) is rating scale used to identify children with autism and distinguishing them from those with other developmental disorders. It includes 15 items that are rated by direct behavioral observation and has been empirically validated.

Differential Abilities Scale-Second Edition (DAS-II): The DAS-II is a standardized test that measures an individual's General Conceptual Ability (GCA) and yields a standard score (M=100, SD=15). It consists of several subtests measuring Verbal Ability, Nonverbal Reasoning Ability, and Spatial Ability and can be administered to children between the ages of 2 years, 6 months and 17 years, 11 months. The results of this test are used to identify a child's cognitive strengths and weaknesses across a wide range of domains that are relevant to development and learning. This assessment takes between 30-50 minutes to complete.

The Mullen Scales of Early Learning assess cognitive and motor ability. Five scales – Gross Motor, Visual Reception, Fine Motor, Expressive Language, and Receptive Language – are used for targeting strengths and weaknesses in children. Included in the questionnaire are three different forms depending on the age of the participant; a 15 minutes test for 1-year old participants, 25-35 minutes for 3-year old participants, and 40-60 minutes for 5-year old participants.

Participants who are older than 5 (the ceiling of the Mullen) but with an apparent cognitive level below the floor of the DAS will receive a Mullen.

Child Symptom Inventory (CSI; Gadow et al., 2002): The CSI is a 132-item, DSM 5 based checklist that asks parents to rate the severity of symptoms on a four-point scale ranging from 0 (never) to 3 (very often). Scores of 2 or higher are usually regarded as a positive symptom. The CSI will assist with the identification of DSM 5 diagnoses other than ASD.

Vineland Adaptive Behavior Scales (VABS-III Survey Interview Form Sparrow, Balla, Cicchetti, 1984): This instrument measures adaptive behavior and yields a standard

score in four domains— Communication, Daily Living, Social, and Motor, as well as an Adaptive Behavior Composite. Adaptive functioning is a core component of an ASD diagnosis and includes toileting skills.

Medical and Psychiatric History Review: This NDAR caregiver questionnaire covers the child's prenatal, perinatal, and postnatal health problems. This information will be used to identify past or current major medical or psychiatric problems that would be incompatible with the study.

Behavior Problems Inventory-01 (BPI-01): This caregiver completed inventory of problem behavior asks caregivers to indicate the frequency and severity of 52 forms of problem behavior most commonly exhibited by individuals with ASD or other developmental disorders (Rojahn, Matson, Lott, Esbensen, & Smalls, 2001). Specific problem behaviors are grouped into three categories (self-injury, stereotyped behavior, and aggressive/destructive behavior). For each individual problem behavior, a caregiver rates the behavior in terms of frequency from "0 – Never" to "4 – Hourly", and the severity from "1 – Slight" to "3 – Severe". We will use this inventory to identify problem behavior that may exclude participation because of its likelihood of interfering with MIE.

Globally Unique Identifier (GUID): This form gathers demographic information that is used to generate a unique identifier, which allow for the use of de-identified data in the rest of the study.

Constipation Status: This will be determined during the medical screening by a licensed and board-certified pediatric gastroenterologist or a nurse practitioner in consultation with a board-certified pediatric gastroenterologist using the criteria below, which are based on the Rome III criteria (Tabbers et al., 2014):

> 2 of the following must occur for a participant to meet criteria for being constipated

1. ≤ 2 defecations per week
2. History of excessive stool retention, including retentive posturing or excessive volitional stool retention
3. History of painful or hard bowel movements
4. Presence of a large fecal mass in rectum
5. History of large-diameter stools that may obstruct the toilet
6. History of irritability, decreased appetite, and/or early satiety, which may disappear immediately following passage of a large stool

≤ 2 of the above will serve as an indicator that the participant is not constipated

We have made two modifications to the published criteria: First, we have eliminated the requirement of a developmental age > 18 months [RATIONALE: this criterion is included in the original definition to account for an expectation that the individual has already achieved independent bowel continence. However, participants in this study will have not yet achieved continence, so developmental age distinction is unnecessary];

Second, we have added the sixth criterion above [RATIONALE: many children with ASD will lack the verbal skills to self-report pain or discomfort due to constipation (Criterion #3). Thus, the symptoms described in Criterion #6 will serve as replacement indicators of constipation for these participants.]

Dependent Measures

Continence: Defined as 60% of days are continent days and no more than 1 day of incontinence over a 7 day period or no more than 2 days of incontinence over a 14 day period based on parent report. This definition is stricter than what has appeared elsewhere in the literature (e.g., Blum et al., 2004) in that it allows for less frequent incontinent bowel movements and also includes a requirement that the participant also have continent bowel movements. The latter requirement is included because children with ASD and encopresis are more likely to be constipated, and so a lengthy period without a bowel movement alone should not be considered an indicator of treatment success. Caregivers and therapists will collect daily data on each of the participant's bowel movements in terms of: (a) continent vs. incontinent, (b) self-initiation (the participant spontaneously using or requesting to use the bathroom), and (c) date and time of the bowel movement.

Toileting independence: Caregivers and therapists will record whether medical intervention was required to elicit any bowel movements, and if so, which medication (e.g., glycerin suppository vs. bisacodyl). A continent bowel movement without the use of any medications will constitute an independent bowel movement, and is an important measure of treatment success. A child will be considered independent in toileting if they exhibit continent bowel movements without the use of medication for 60% of days with no more than 15% incontinent days based on parent report.

Parent target problem (PTP): At baseline, an independent evaluator (IE) will use the PTP interview to record the caregivers' estimate of the frequency of incontinent bowel movements and the impact of their child's encopresis on their family. From this description, the IE (who will be blind to treatment assignment) will generate a brief narrative describing the participant's encopresis and its impact. The IE will read this narrative back to the caregiver and ask him/her to provide corrections and/or add any pertinent missing information. This process will continue until the caregiver reports that the narrative is an accurate description. This narrative and all available information collected at baseline (caregiver collected home data, Vineland, etc.) will be used by the IE to rate the overall severity using the 7-point, Clinical Global Impression for Severity (CGI-S; Aman, Bailey, & Lord, 1985). At the conclusion of the clinic-based phase of treatment (Week 4), and again after follow up (Week 28), the narratives will be reviewed with the caregiver, revised by the IE, and integrated with all available information to rate the Improvement scale of the Clinical Global Impression (CGI-I; Busner & Targum, 2007). The CGI-I is a 7-point scale with anchors including 1 (Very Much Improved), through 4 (No Change), and 7 (Very Much Worse). By convention,

ratings of Much Improved and Very Much Improved define positive response. We have already begun to train the IEs to reliability on the CGI and recording of PTPs. In addition to ratings by the IE in real time, at the end of the trial, a panel of judges, who are blind to group assignment, will review the narratives at baseline (Week 2), endpoint (Week 8), and follow-up (Week 28). The change from baseline to each subsequent time point will be independently rated by the panel of judges on a 9-point scale (where 5 = no change, 4 = minimal improvement, 3 = definite improvement, 2 = much improved and 1 = very much improved; scores of 6 through 9 follow the same pattern in the worsening direction). Our team has used this approach in prior studies (Arnold et al., 2003; McGuire et al., 2014), and have shown that a panel of judges is highly reliable and that this method is sensitive to treatment effects.

Parenting Stress Index (PSI; Abidin, 1995): This is a 36-item parent-completed questionnaire (short form) for families of children 12 years of age and younger. It has been empirically validated. The PSI has three scales: Parental Distress, Difficult Child Characteristics, and Dysfunctional Parent-Child Interaction. The 36-item PSI has been used in several studies by RUPP Autism Network.

Caregiver Strain Questionnaire – Short Form (CGSQ-SF; Brannan, Heflinger & Bickman, 1997): This questionnaire measures the impact of having a child with ASD in the family. The questionnaire includes 7 items that assess three dimensions of caregiver strain: objective strain, internalized subjective strain, and externalized subjective strain. Each item is rated on a 5-point scale ranging from 1 (not at all a problem) to 5 (very much a problem).

Treatment Acceptability Rating Form-Revised (TARF-R; Reimers & Wacker, 1992): The TARF-R is a 20 item measure of treatment acceptability that is completed by caregivers following completion of either MIE or TAU. It will be administered at the Midpoint (Week 4) and Endpoint (Week 8). The survey takes approximately 5 minutes to complete.

Aberrant Behavior Checklist (ABC): The ABC is a 58-item parent-report measure with five subscales: *Irritability* (includes agitation, aggression and self-injurious behaviors, 15 items); *Social Withdrawal* (16 items); *Stereotypies* (7 items); *Hyperactivity* (16 items); and *Inappropriate Speech* (4 items), (Aman et al., 1985, Aman et al., 1987). The ABC is commonly used in clinical trials in children with ASD (Aman et al., 2009; King et al., 2009; RUPP Autism Network, 2002 and 2005). The use of the ABC in the current study will permit easy comparison of the study sample to subjects in past studies. It will also be used as an exploratory outcome measure.

King's Stool Chart (KSC): The King's Stool Chart is a visual guide characterization of fecal matter into 12 different categories based on consistency, texture and size. It has been validated for use in free-living individuals as well as patients with various GI issues.

Study Drug and Dosing

The study involves the use of two medications: a Glycerine and Bisacodyl suppository. Glycerin suppositories are composed of a hyperosmotic agent consisting of glycerin (active ingredient), purified water, sodium hydroxide, and stearic acidand. Bisacodyl is a derivative of triphenylmethane consisting of Bisacodyl (active ingredient), acadia gum, ammonium hydroxide, beeswax, carnauba wax, D&C Yellow #10 aluminum lake, D&C Red #30 aluminum lake, glycerin, glyceryl monostearate, iron oxide, lactos monohydrate, magnesium stearate, methacrylic acid ethyl acrylate copolymer, methyl paraben, modified corn starch, polyethylene glycol 6000, polysorbate 80, povidone, propyl paraben, shellac, sodium benzoate, sucrose, talc, titanium dioxide, and triethyl citrate. Both these medications are available over the counter.

Medications will be dispensed quarterly by the Children's Healthcare of Atlanta Research Pharmacy and stored on site in a locked cabinet in the nurse's office at the Marcus Autism Center. Both types of suppositories are sealed in plastic (PVC/PE) cavities within a cardboard carton in pack quantities of 12. Consistent with manufacturer recommendations, the cabinet in which these will be stored will remain dry, below 25°C, and away from direct light. A medication log will be maintained to track each dose removed from storage and administered as part of the study. This log will include the following information: date, time, participant, and dose. See Table 3.0 below.

Table 3.0 - Doses of Liquid Glycerin Suppositories by Age and the Single Strength of Bisacodyl

Drug	Suppository Dose	Ranges allowed
Liquid glycerin suppository	Children age 2-5 years: 4 ml/applicator[1]	Children 2-5 years: 1 dose per day or as directed
Liquid glycerin suppository	Children age 6-12 years: 7.5ml/applicator[1]	Children ≥6 years: 1 dose per day or as directed
Bisacodyl suppository	5 mg[2]	Children 2–10 years: 5 mg/day Children >10 years: 5–10 mg/day

1. Recommended by the manufacturer

2. Tabbers MM, DiLorenzo C, Berger MY et al. (2014) *Evaluation and Treatment of Functional Constipation in Children*: Evidence-Based Recommendations from ESPGHAN and NASPGHAN. J Pediatric Gastroenterology and Nutrition, 58(2): 258-274.

A trained therapist will administer the liquid glycerin suppository as recommended by the manufacturer via the rectum using the following dosing recommendations: 7.5ml (Fleet Adult Liquid suppositories) or 3.5ml4 ml (Fleet PediLax) pediatric size given to participants 2-5years old; adult size given to participants ≥ 6yo. When bisacodyl is used the following dosing recommendations will be followed: 5 mg for all participants (administered via the rectum). Depending on when or if the participant has a bowel movement (see intervention section) participants may receive between 0-2

suppositories per day. Participants will never receive two of the bisacodyl suppositories. However they may receive two of the liquid glycerin suppositories or one of each in a given day. We will ensure that all participants keep concomitant medications stable and to notify us if this is not the case during the study.

Part of treatment may involve physical management of participants, such as to address problem behavior (e.g., aggression, disruption, self-injury) to ensure the safety of participants, caregivers, and the therapist. Therapists are trained and will implement personal protective procedures (e.g., blocking hits, releasing grabs) if the participant is aggressive (hurting others) to minimize any harm, prioritizing the safety of the participant. In addition, the below procedures may be used as needed.

- Prompting procedures: to gently guide the participant to sit on the toilet, or to prompt him or her to engage in redressing or hygiene tasks. This may involve hand-over-hand physical guidance.

Emergency restraint: If a researcher determines that a participant cannot be kept safe by any other means, they will implement an emergency restraint procedure. This will be done only until it is deemed that the participant is safe. If a caregiver is not there to observe the procedure, the caregiver will be notified by the researcher as soon as possible that this procedure occurred. A licensed psychologist is consulted for any restraint procedure used.

Home Implementation - After the MIE treatment phase, subjects will be given suppositories to utilize at home and a handout that addresses frequently asked questions about the use of suppositories. MIE treatment group subjects will leave with one of three planned regimens: one Glycerin suppository a day, two Glycerin suppositories a day or one Bisacodyl suppository a day. The determination of which group subjects are in will be made by the study team based on subject's response during MIE treatment. It is anticipated that most subjects will leave with the plan of one Glycerin suppository a day. Subjects in both the one Glycerin or one Biscaodyl suppository a day will be given a 30-day supply of study medication upon completing the MIE treatment phase (e.g. 30 suppositories). Subjects receiving two Glycerin suppositories a day will leave with enough medication to also last 30-days while taking two Glycerin suppositories (e.g. 60 suppositories). Note that subjects in the two Glycerin suppository group may only need to receive a single suppository if the child begins to have bowel movements after administration of one suppository.

Intervention Content

MIE consists of daily clinic appointments, each of which lasts until a bowel movement occurs or 3 hours elapse. Each appointment consists of a series of scheduled sitting routines (i.e., "sits") that last up to 32 min. Each sit consists of 10 min on the toilet, followed by 1 min of standing, then repeating the 10 min on the toilet 1 min off, for 30 cumulative minutes of sitting. The first sit is conducted prior to the administration of any medication to provide an opportunity for an independent continent bowel movement. If no continent bowel movement occurs, trained staff administer a dose of

a liquid glycerin suppository to elicit a bowel movement, immediately followed by another sit to ensure any resulting bowel movement is continent. Any continent bowel movements result in immediate delivery of a potent positive reinforcer, identified previously via systematic preference assessments (Deleon et al., 1996). The appointment ends following a continent bowel movement. If a bowel movement is not observed the participant receives a 30 min break, followed by a second dose of the glycerin suppository. The participant is once again guided to complete the sitting routine following the second administration, with the same consequences for continence. After the third sit the appointment ends even if a continent bowel movement did not occur. Glycerin suppositories are replaced by bisacodyl if 2 or more days pass without a continent bowel movement using the liquid glycerin suppository. If bisacodyl is required it is administered prior to the second sit (i.e., after no bowel movement occurs on the opportunity for independent continence) to ensure that the medication has sufficient time to work prior to the end of the appointment. Medication fading occurs each time there are two consecutive days with continence by replacing bisacodyl with a glycerin suppository (if bisacodyl was necessary), and/or reducing the dose of the glycerin suppository by 50% until continent bowel movements occur independently during the first sit (i.e., without medication). Caregivers are trained to implement the toileting routine during the final two days of MIE until they demonstrate 90% fidelity with the protocol. Upon completion of MIE they are instructed to continue to implement the intervention until independent continence is achieved.

Subjects receiving MIE will be expected to receive a minimum number of treatment appointments prior to ending the MIE treatment phase. Subjects in the 2-week MIE treatment group will be expected to complete 10 MIE appointments within 17 days. This will ensure all subjects received an adequate level of treatment intervention prior to receiving parental intervention exclusively at home. Subjects who do not meet the minimum number of appointments within the time frame will be documented as protocol deviations.

Inclusion & Exclusion Criteria

Inclusion Criteria

1. Males and females ≥ 5 years of age and ≤ 12 years 11 months of age.

2. DSM-5 diagnosis of *Autism Spectrum Disorder* as established by clinical assessment, corroborated by the Autism Diagnostic Observational Schedule, Autism Diagnostic Interview-Revised and/or Childhood Autism Rating Scale-Second Edition.

3. Fewer than 60% of days are continent days or more than 1 day out of 7 is an incontinent day over the previous 7 days (a continent day is defined as a day with at least one continent bowel movement. An incontinent day is a day with an incontinent bowel movement regardless of whether a continent bowel movement also occurs).

4. Medication free or on stable medication (no changes in past 6 weeks and no **planned** changes for the next 6 months) [RATIONALE: Inclusion of children on stable medication

eliminates a potential confounding variable and enhances the generalizability of study findings].

5. Urine continent – Over half of the voids are continent when the child is with the parent and when the child is on a typical toileting routine.

Exclusion Criteria

1. Presence of a known medical condition in the child (based on medical history or physical examination by a gastroenterologist or nurse practitioner working in consultation with a gastroenterologist) that would interfere with child's ability to control his/her anus. These include:

- History of any anal surgery
- Spinal dysraphism (e.g., spina bifida)
- Other neurologic disorder affecting anal function
- Prolonged/recurrent gastrointestinal infectious disease (e.g. Clostridium dificile colitis)

In addition, the following may constitute exclusions following evaluation by a physician:

- Inflammatory bowel disease
- Short gut syndrome
- Chronic diarrhea
- History of intestinal/abdominal surgery

[RATIONALE: inability to control the anus is highly likely to prevent the success of any treatment for encopresis. All medical conditions will be reviewed by study team to make a final determination of eligibility.]

2. Presence of a current serious behavioral problem or psychiatric condition that would require another treatment (e.g., psychotic disorder, major depression, moderate or greater aggression, severe disruptive behavior), based on information collected at screening and the Behavior Problems Inventory-01 (BPI-01; as described below). [RATIONALE: presence of an untreated serious behavioral problem or psychiatric condition would interfere with the child's ability to participate in the treatment.]

3. Currently receiving and caregiver refusal to discontinue ongoing behavioral or alternative medical intervention for encopresis [RATIONALE: presence of other ongoing treatments would confound results of this study.]

Exceptions to Inclusion and Exclusion Criteria

These inclusion and exclusion criteria reflect our best estimate for subject selection in this clinical trial. In our past trials in children with ASD, we have encountered a few subjects who did not satisfy all selection criteria, but, in the judgment of the research

team, appeared appropriate for the study. For example, a healthy child with a developmental disability who was not toilet trained could not provide a urine sample. Therefore, we could not say with certainty that his urine test was "normal." To exclude such a child would threaten the application of the study findings to lower functioning children. In the event of a need to consider a potential exception to the inclusion/exclusion criteria the case panel (e.g., Drs. Call, McElhanon, Lomas-Mevers, Scahill) will review the case and decide whether to enter a child with findings that challenge application of entry criteria. In making such decisions, the case panel will insure that the exception 1) does not decrease the benefit-risk ratio for the subject in question; 2) does not compromise the scientific integrity of the study; and 3) does not depart from good clinical practice. Such exceptions and rationale will be documented on a case report form.

Risk of Participation

Potential risks and discomforts associated with this study include:

- The primary risk to participation in the study is in the area of participant confidentiality. A number of safeguards will be put in place to protect the privacy of participants and confidentiality of data, which are described more fully below within "plans for data management and monitoring".
- Some participants may experience distress when separating from caregivers and/or during study procedures, which include requiring the child to remain seated on a toilet for up to 30 minutes at a time and administration of suppositories.
- The medications to be administered are over-the-counter, are dosed as on packaging, and used under protocol created by a pediatric gastroenterologist. They represent no more risk than listed on Children's Healthcare of Atlanta Lexicomp® formulary: Glycerin suppository adverse reactions are abdominal cramps, rectal irritation, and tenesmus. Bisacodyl adverse reactions listed are labeled rare and apply to oral and rectal preparations: abdominal cramps (mild), electrolyte disturbance (metabolic acidosis or alkalosis, hypocalcemia), nausea, rectal irritation (burning), vertigo, and vomiting. Additional steps to be taken to minimize risks of distress to participants include providing them with preferred items during separation from caregivers. In addition, if a participant exhibits significant distress during study procedures they will be discharged from the study.

Benefits to Subjects

Participants in the proposed study will receive compensation for participation in the amount of $10 for each week of data collection, comprising a total of $100. In addition, participants may learn to have predicable bowel movements in the toilet.

Setting

The study will take place at the Marcus Autism Center. Caregivers of children meeting inclusion criteria will be invited to give informed consent for inclusion of their

child in the study. The experimental sessions will be conducted in private client restrooms at the Marcus Autism Center.

Recruitment

The Marcus Autism Center currently sees approximately 5,000 unique patients annually who may be eligible to participate in this study, including a number of families who have already requested the opportunity to participate. A clinician will contact families (via phone, email, or face to face) currently waiting to receive services for encopresis to explain the research opportunity. Then, if parents are still interested in participating with their child, they will be asked to provide basic information by telephone regarding their child's difficulties via the Oral Consent and HIPAA Authorization Script and Information Sheet For Research Study Screening) to determine if they meet the eligibility criteria for the study. Flyers will also be posted throughout Marcus, on the Marcus website, and social media to help with recruitment.

Some participants may have a history of engaging in problem behaviors including, but not limited to, aggression, destructive behavior, self-injury, running away, or dropping to the floor. All members of the study team who interact with participants are trained in the Marcus Crisis Prevention Program, which consists of protective procedures in order to safely manage problem behavior. When obtaining informed consent for participation in this study, the person obtaining consent will also describe the protective procedures and emergency protocols to the family. The consent forms giving permission to use those procedures are the same as those used with clinical families. Low-intensity problem behavior will be managed within the context of the study, but more serious problem behavior will result in the study team discontinuing study procedures temporarily in order to safely manage problem behavior and may be reported to the IRB.

A total of 150 participants will be enrolled in the study and randomly assigned to one of three groups (60 in 2-week MIE, 60 in 1-week MIE, and 30 in TAU group). Starting year 3 a total of 112 participants will be enrolled in the study and randomly assigned to one of two groups (56 in 2-week MIE and 56 in TAU group). We will recruit the necessary sample over a 4-year period, with 19 participants enrolled in Year 1 to allow for ramp up, and 22 in Year 4 to leave sufficient time for participants to complete 3-months of caregiver implementation prior to follow-up and for data analysis. We will recruit 35 participants in Year 2 and 45 in Year 3.

Years	Year 1				Year 2				Year 3				Year 4			
Months	1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30	31-33	34-36	37-39	40-42	43-45	46-48
n per period	3	7	4	5	6	8	12	9	9	9	9	9	9	9	4	completion
Cumulative N	3	10	14	19	25	33	45	54	63	72	81	90	99	108	112	∑ = 112

Families will be asked to provide basic information by telephone regarding their child's difficulties via the Oral Consent and HIPAA Authorization Script and Information Sheet For Research Study Screening to determine if they meet the eligibility criteria for the study.

Training

Sessions will be conducted by research personnel at the Marcus Autism Center who have significant experience delivering clinical care to children with ASD and/or facilitating research participation by children with ASD. Training includes basics of behavior analysis, data collection, and protective procedures. Staff members are supervised by a doctoral level behavior analyst and licensed psychologist. Following treatment, staff members will train caregivers to implement the treatment with at least 90% fidelity.

Informed consent

Caregivers of children who meet inclusion criteria of the current study will be verbally invited to consent to have their child participate in the study using lay language. If the caregiver expresses assent and wishes to learn more about the study, he or she will be presented with a typed copy of the consent form, which will be explained to them by the study coordinator, principal investigator, or research assistant in greater detail. Assent will not be obtained from the children with developmental disabilities included in the study. Based on historical data and the population served at the Marcus Autism Center, caregiver consent is required in all cases for the individuals with disabilities (i.e., these individuals with developmental disabilities do not possess the pre-requisite communication skills to give assent). Because children with developmental disabilities often lack the capacity to grant assent for participation, the research study cannot be carried out without a waiver of child participant assent. Each child's participation in the study involves a minimal risk of harm.

Caregivers will be informed of confidentiality procedures, the rights of children participating in the study, plans for data management and monitoring, and also that their decision to have their child to participate will not influence the quality of services that they will receive at the Marcus Autism Center. Additionally, caregivers will be told that they will receive compensation for their participation and that they may withdraw any or all responses from the study at any time. Caregivers will review a printed copy of the consent form as well as the contact information for the principal investigator and the project coordinator.

Withdrawing Participation: Parents are free to withdraw from the study at any time. This will be clearly stated during the consent process. Parents who indicate intention to withdraw from the study will be offered to confer with the study team to discuss the matter. If the discussion indicates that the child needs another treatment, we will assist the family in locating that treatment. Parents who are willing will be invited to return for

child assessments. Data from children who drop out of treatment, but return for assessments, will be analyzed in the originally randomized group.

Plans to inform participants of new findings

Because this study is an evaluation of the efficacy of a novel intervention for encopresis and to demonstrate the feasibility of the intervention, the caregivers will receive periodic updates regarding progress made throughout the study. They will also be informed of any new information that the study team may become aware of during the study.

Compensation

Parents will be offered $10 for each week of data collection for a total of $100

Confidentiality

Participants will be de-identified during the data collection and analysis procedures, with each participant randomly assigned a study identification number (DEX ID). Only the authorized study personnel will have access to the codes that link identifiers to participants. These codes will be stored on a password protected, secured server located at the Marcus Autism Center (Marcus Data Exchange or DEX).

Case report forms (CRFs) contain the subject's DEX ID number – but no identifying information. DEX is a secure, password protected data base. The folders containing CRFs data will be kept in locked files and access to these files is only granted to members of the research team.

Access to study records (case report forms) will be restricted to study staff. To maintain the treatment blind, the independent evaluators will keep records in a separate folder from the unblinded staff. Others that have access to the record include individuals with regulatory responsibility at Emory, Children's Health Care of Atlanta (CHOA). All clinical trials are subject to routine audits by offices at Emory or CHOA.

Data storage

The data management system has several features designed to protect confidentiality such as "role-based" user privileges. For example, individuals can be allowed 1) "read only" access to study data, 2) "read/edit" access, 3) to see only certain case report forms, and/or 4) to run reports or export data for analysis. The data system maintains an electronic audit trail of all modifications to the data base, including the user who made the change, the date and time, and the previous value and new value of the data point.

The research coordinator will enter data on the DEX web site. All data are double-entered (with an automated validation check comparing the two entries for errors). Only staff members trained in the DEX system have access to data entry (password protected). The progress of data collection is monitored with web-based electronic data

form reports, which will produce a profile of all forms expected and received for each study subject. Missing-forms reports are electronically accessible by the data manager and the coordinator. All studies follow informatics standard operating procedures and produce monthly reports on audits conducted to examine study fidelity and data quality. These audits are conducted by an assigned data manager from each study. Outliers and unusual values will be checked for accuracy. Data questions or problems will trigger queries back to the study team to assure that all forms are entered and available for analysis. Recurring problems with the data entry system will be resolved via discussion between the data manager and coordinator and PI as necessary.

REDCap Utilization: REDCap (Research Electronic Data Capture) is a web-based application used to create forms and manage databases in order to support data capture and surveys for research studies. Participants will be given the option to sign the consent and study measures using the REDCap link to the specific survey(s). Forms will be delivered to the participant via an email to the parent with a unique link to complete online. Participants will continue to have the option to fill out forms by hand (in-person, by phone, mail, email).

Analytic plan

During the trial, the statistician will monitor missing data and errors, enrollment and attrition. When the trial is completed, descriptive statistics will be calculated for baseline data across treatment groups. Additional analyses will be undertaken to inspect data for errors, inconsistencies, and incomplete information across time points. This will include examining the data with simple frequency tables and scatter plots. Data anomalies and outliers will be examined and corrected if necessary. These preliminary analyses will include descriptive statistics in each treatment group for all outcome variables, plots of longitudinal data over time, and examination of distributions within groups at important nodal points (e.g., Baseline, weeks 2, , 4, 8, 28). All the analyses will apply the *intent-to-treat* principle. For modeling and hypothesis testing, the proposed likelihood-based approach regards missing data as missing at random (MAR; i.e, missing data are independent of unobserved data). Although there is no proven method for verifying the MAR assumption, the likelihood-based solutions are robust to violations of ignorable missing data (i.e, situations where the MAR assumption is not met). Nevertheless, prior to analyses for efficacy, we will examine the frequency, reasons, pattern and time to dropout and missing values across treatment groups. If substantial differences in missingness occur across treatment groups that cannot be adequately explained by observed variables, secondary sensitivity analyses will be performed. These techniques will be considered cautiously in our analyses as they require certain assumptions that cannot be evaluated from the data under analysis. Statistical significance will be assessed at the 0.05 level unless otherwise noted. All analyses will be conducted using SAS v9.4 for Windows (Cary, NC, USA).

Primary outcome: A Chi-square test will be used to compare the proportion of children who achieve continence (60% of days are continent days and no more than 1

incontinent day over a 7 day period and no more than 2 incontinent days over a 14 day period) based on parent report at Week 8 (endpoint of acute randomized trial). The contrast will be MIE-2 vs TAU.

Secondary Outcome #1: A Chi-square test will be used to compare the proportion of children who are rated by the Independent Evaluator as *Much Improved* of *Very Much Improved* on the CGI-I at Week 8. The contrast will be MIE-2 vs TAU.

Secondary Outcome #2: ANCOVA will be used to compare change in parental stress and strain from baseline to Week 8 as measured on the Parenting Stress Index and the Caregiver Strain Questionnaire. The contrast will be MIE-2 vs TAU.

Sample Size and Power Calculation for Primary Outcomes. As noted above, we will perform one planned pairwise comparison for the primary outcomes at Week 8: MIE-2 vs TAU. We set our significance level for alpha as 0.05 to control the family-wise Type I error rate at the 5% level. Based on our pilot data, we conservatively estimate the following rates of children achieving continence at Week 8: 10% of participants in TAU, 75% of those in the MIE-2 group and 50% for the MIE-1 group. With a sample size of 54 in each of the TAU MIE groups, we can detect a 29% difference in response rate on our primary categorical measure with 15% dropout rate and type I error rate of 0.05. We propose that this will be a valid test of the Two-week medical-behavioral intervention, which was, and remains, the primary aim of the study.

Data Security

Electronic Protected Health Information (ePHI) is carefully guarded within the database. All full and incremental database backups are compressed and encrypted before being sent using secure sockets layer (SSL) to a secure, geo-redundant backup infrastructure. All communication with the server for normal usage, maintenance and backups is encrypted using SSL.

The DEX database has the following Security features:

Hot Security The server runs a highly secure operating system (FreeBSD), providing immediate resistance to many common attacks and exploits. A unique web-server is used to reduce system exposure to attacks. The web server is written in a high-level language that substantially reduces the effectiveness of most common attacks (such as buffer-overflows). All communication between the site server and remote workstations (any modern computer capable of running the Firefox web browser) is logged and uses SSL encryption. The system fully supports journaling to ensure data integrity, to support audit trails, and to simplify disaster recovery. Furthermore, all collected data, as well as the journal itself, can be mirrored (in encrypted form) on redundant remote servers. In the rare case that the server is compromised, any modification to system resources can be undone by simply contacting Prometheus Research, who will restore the system from backup.

Cold Security RexDB® servers employ twin mirrored and encrypted hard drives to prevent data access should the server ever be stolen or compromised. This also virtually eliminates downtime should one drive fail. All RexDB® backups are stored on servers kept in locked racks in physically secure locations.
In all studies, the database is maintained within the existing data management system providing high degree of security and quality monitoring. Data are backed up according to the following specifications:

Remote Backups Secure, automated backups of all server data are provided using a redundant infrastructure of Tarsnap.com and hosted servers. All data are encrypted using asymmetric keys before leaving the site server. All data are sent securely via an OpenVPN and SSH connection to the remote backup server. The decrypt key is kept on neither the site server nor the backup server; instead, it is stored locally on a separate server.

Frequency of Backups Nightly system backups are archived for seven days; weekly backups are archived for four weeks; monthly backups are archived for as far back as space will allow. Incremental (binary) backups of all database changes occur every 15 minutes; the write-ahead log monitors incremental changes in the interim and increases backup frequency under heavy usage.

Data Sharing During the consent process, we will explain to parents that data collected in the study is for research purposes and that research records will not be merged with medical records. The exception to this is the visit to the gastroenterologist/nurse practitioner. This visit is considered standard clinical care and therefore it will be uploaded to their medical record. Further, data collected in the study or the results of tests conducted in the study can be obtained by the parent.

Adverse Event Collection and Reporting
The IE will monitor adverse events – whether related to the study treatment or not. Adverse events will be documented according to onset, offset, severity and action taken. The Safety Review also enquires about concomitant treatments that will be documented as needed.

If questions arise about a subject's possible deterioration, the situation will be discussed at the weekly team meeting. If the team determines that the subject's symptoms are becoming distressing or dangerous, we will hold a clinical conference with the participants caregiver and determine the best course for the subject. This may include withdrawal from the study in order to institute a treatment plan.

NOTE: In keeping with the intention to treat principle, we will ask parents of subjects who withdraw from treatment to return for study assessments and the subject's data will be analyzed with the original randomized group.

Safety Review: A safety review for adverse effects and concomitant medications will be conducted at baseline and every assessment visit by the IE. To accomplish this systematic review, the IE will use the Safety Review Form that has been used in several multi-site clinical trials in children with ASD. It contains a general inquiry about the child's health complaints, medical visits and new medications, and several questions about daily activities (e.g., sleep, appetite, energy level, and bowel and bladder functions) since the last study visit.

New adverse events (whether considered related to the treatment or not) will rated mild, moderate or severe. The ratings: mild, moderate or severe are defined as follows:
mild= present, but no intervention required;
moderate=present, may be bothersome or may require intervention;
severe=present, bothersome and requires intervention.

All **new** adverse events (mild, moderate or severe) will be documented on the adverse event log. The status of previously-reported adverse events will be monitored as well. The adverse event log requires the independent evaluator to label the AE (a list of preferred terms will be provided) and to document the severity, onset, course, outcome, and attribution.

Decisions on the appropriate care of the subject will be made by the independent evaluator (who will be blind to treatment assignment) and the PI and in collaboration with the family's primary care provider as needed.

The attribution of reported AEs will be classified as follows:
- Definite: AE is clearly related to the study participation.
- Probable: AE is likely to be related to the study participation.
- Possible: AE may be related to the study participation.
- Unlikely: AE is doubtfully related to the study participation.
- Unrelated: AE is clearly not related to the study participation.

Serious adverse events: A serious adverse event (SAE) is defined as one that poses a threat to the participant's life or functioning. We note that "severe" is not equivalent to "serious." A severe rash may not be a serious adverse event, whereas a heart attack of any severity is likely to be a serious adverse event. An SAE is defined as an event that entails one of the following:
- Death;
- Threat to the individual's life;
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability or incapacity;
- Intentional drug overdose;
- Any other significant event that jeopardizes the participant.

Routine reporting of AEs will be documented on the Adverse Event Log as described above. All AE data will be captured in the electronic database and reviewed by Drs. Call and McElhanon every 6 months. AEs occurring at a greater than expected frequency or severity will be reviewed with the Steering Committee (Drs. Call, McElhanon, Lomas-Mevers, Scahill and McCracken). Investigators will provide this information to the Emory IRB according to IRB Policy & Procedures. The Steering Committee will decide if modifications to the protocol or consent form are required.

Reporting of Serious Adverse Events (SAE). If an adverse event meets the definition of an SAE, the PI in consultation with Dr. McElhanon (and Steering Committee if needed) will determine whether the SAE is possibly, probably of definitely related to the study intervention. The PI will report SAEs to the IRB and the funding agency within 10 days of the determination that the event meets one of these criteria: a) serious AND unanticipated AND possibly, probably or definitely related events; and b) anticipated adverse events occurring with a greater frequency than expected.
Serious adverse events that do not meet any of these circumstances will be reported with IRB re-approvals.

Data Safety and Monitoring Plan
The study will be conducted in accordance with "good clinical practice" as outlined in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (Dixon & Hallinan, 1999).

The study team will meet weekly and decisions will be made by consensus. The study team will provide oversight and ensure that the study is conducted in accordance with the protocol. The coordinator and the statistician have direct access to the PI if data quality or data safety issues emerge from reviews conducted by either the coordinator or the statistician.

The statistician will serve as an independent monitor of data quality and safety with input from study team. The statistician will have direct access to the data base to provide an additional check on missing data, attrition, adverse events and treatment response. As a single site study in a population that is well known to the clinical research team at Marcus, we do not see a need for an external Data and Safety Monitoring Board. The statistician will review the data set every six months. Questions and concerns will be brought to the study team and PI. To protect the blind, treatment assignment will not be divulged. The discussion with the study team is likely to focus on individual cases and overall trends. Given the sample size of 138(updated from 150), we have not declared any stopping rules for benefit or futility. In the highly unlikely occurrence that adverse events show group differences, the study team will seek advice from the Marcus Center Director, Dr. Ami Klin. He is supportive of the study, but not directly involved.

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