

February 8, 2018

EMOTIONAL AWARENESS AND SKILLS ENHANCEMENT PROGRAM
(EASE)

Study Protocol and Statistical Analysis Plan

1. PROJECT NARRATIVE

1.A. Overview

Persistence of autism spectrum disorder (ASD) into adolescence and adulthood, along with increased identification, are contributing to a steadily growing population of adolescents and adults with ASD (Seltzer et al., 2004). Life-time societal costs of ASD have been estimated to be \$3.2 million per individual (Ganz, 2007). Of all the factors that contribute to this cost estimate, lost productivity and adult care are the largest (Ganz, 2007). The successful transition to adulthood is largely dependent on the foundation set in adolescence (Arnett, 2000), yet many youth with ASD decline in functioning during adolescence (Picci & Scherf, 2015). This decline is at least partly due to impaired emotion regulation (ER), defined as the ability to modify one's arousal and emotional state to promote adaptive behavior. Impaired ER, often evident early in life in ASD, may become exacerbated in adolescence due to increasing social demands (Mazefsky & White, 2014a). ER impairment contributes to negative social outcomes (e.g., via reactive aggression, hostility), which in turn leads to negative expectancies for future interactions and a cycle of social avoidance, missed opportunities, and failure to learn new social skills as well as, ultimately, poor quality of life marked by limited independence.

Consistent with the scientific literature outside of ASD (Aldao et al., 2010), there is now evidence that impaired ER is associated with a range of problem behaviors and comorbid symptoms in ASD, including depression, aggression, and anxiety (Guy et al., 2014; Mazefsky et al., 2013). In our prior work, we found that impaired ER was consistently identified by parents, students with ASD, and high school and college teachers as a primary barrier to successful transition into college (White et al., 2016). Finally, impaired ER is related to the need for inpatient hospitalizations (Righi et al., 2017).

Although the role of impaired ER in ASD has been increasingly appreciated in the scientific community, translation to clinical practice has not been realized (Weiss et al., 2017). The majority of psychosocial treatment research to address emotional problems has focused on children and the remediation of anxiety. These protocols generally do not address other common problems such as explosive behavior, meltdowns, irritability, anger, and depression - all of which stem from impaired ER. One way to have a broader and more sustained clinical impact is to focus on core processes, such as ER impairment, that underlie a range of problems. Although Cognitive-Behavioral Therapy (CBT) has demonstrated potential for treating anxiety in children with ASD, response has been variable and effect sizes are lower than in non-ASD youth (Kreslins et al., 2015). No work to date has attempted to address ER impairment in adults with ASD, leaving the largest and fastest growing autism population without treatment. Given the role that ER impairments play in contributing to social impairment, comorbid psychiatric symptoms, and poor functional outcomes, it is an ideal underlying process to target in treatment (Weiss, 2014).

In sum, there are very limited treatment options for adolescents and adults with ASD, and no psychosocial interventions to support healthy emotional functioning and reduce problem behaviors that span the transition from adolescence to adulthood. To address this significant treatment need, we developed the *Emotion Awareness and Skills Enhancement* (EASE) Program. EASE is a 16-week individual therapy program for verbal adolescents and young adults with ASD, designed to improve ER capacity. EASE emphasizes awareness of one's own emotional responses as a foundational skill that promotes the ability to manage intense negative emotions, which is taught through mindful awareness. Once increased emotional self-awareness is improved, the therapist works with the client to build his/her tolerance for distress through different strategies for emotion management. Targeting impaired ER during adolescence and young adulthood in ASD should improve psychiatric concerns, problem behaviors, and functional outcomes. This developmental period (ages 14-21) represents a heightened time of risk for emergence of co-occurring mental health problems, and is thus a critical time to intervene. Based on data from a pilot study of EASE, we have evidence that it is both feasible to implement and acceptable to participants; moreover, we have observed improvements in emotional functioning and problem behaviors, and decreased functional impairment. Given these promising preliminary data, the next step is to evaluate EASE's efficacy through a randomized controlled trial.

1B. Emerging adults are understudied and at high risk for poor outcomes.

Although adults are the fastest growing segment of the population of those with ASD, there has been limited treatment research focused on adults (Mazefsky & White, 2014b). A recent review concluded that there have only been 13 psychosocial treatment studies for adults with ASD since 1965, most of which used single case designs (Bishop-Fitzpatrick et al., 2009). The extant research indicates that young adults with ASD who do not have co-occurring intellectual impairment are at heightened risk for poor outcomes such as diminished independence and lower rates of competitive employment (Taylor & Mailick, 2014). Most adults with ASD are neither consistently nor gainfully employed and cognitively able adults with ASD are less likely than peers with other types of disabilities to enroll in postsecondary education (Engström et al., 2003; Wei et al., 2013).

The developmental period bridging adolescence to adulthood is when critical milestones are generally achieved, including increased independence, autonomy, and responsibility (Arnett, 2000). Yet, adolescence is also characterized by heightened reactivity to social and emotional stimuli, which appears to increase the risk of psychopathology (Dahl & Gunnar, 2009; Kessler et al., 2005). Unfortunately, many youth with ASD either fail to meet developmental milestones or decline in functioning during adolescence (Picci & Scherf, 2015). In sum, there is a crisis in our lack of treatment options for teens and adults with ASD, and this project will be one of the first to address this crisis.

1C. The developmental vulnerabilities of adolescence may be magnified in ASD due to a high propensity for ER impairment.

Youth with ASD may be predisposed to impaired ER, which broadly encompass processes related to modifying emotions to fit the context or meet one's goals (Thompson, 1994; Gross, 1998). Although neuroimaging research on ER in ASD is limited, there is evidence that the neural structures implicated in ER in other populations differ in ASD either in function, size, or circuitry with other parts of the brain in ASD (Herrington & Schultz, 2010; Mazefsky & Minshew, 2010; Monk, 2008). High rates of mood and anxiety disorders in the first degree family members of children with ASD, and conceptualization of such problems as part of the broader autism phenotype, raise the possibility of an underlying genetic predisposition to ER impairment in ASD as well (Gerdtts & Bernier, 2011; Mazefsky et al., 2008, 2010). Further, ASD-related characteristics may directly contribute to a failure to recognize when regulatory strategies are needed, such as poor perspective-taking and problem solving, lower response inhibition, deficits in recognizing others' emotions, and misreading social cues (Mazefsky & White, 2014a). In addition, sensitivity to sensory input and change may increase reactivity and lability (Dunn & City, 1997).

1D. ER impairment is associated with a wide range of negative outcomes.

Impaired ER may be partially responsible for problem behavior in ASD, including meltdowns, self-harm, and reactive aggression (e.g., Patel et al., 2016; Pouw et al., 2013; Samson et al., 2015; Ting & Weiss, 2017). Clinically problematic aggression is extremely common, present in approximately 1 in 2 children and adolescents with ASD, and aggression is associated with a host of other problems such as gastrointestinal disturbance, self-injury, and poor social functioning (Mazurek et al., 2013; Saqr et al., 2017). Indeed, aggression is one of the primary drivers of medication use among adolescents and adults with ASD (Saqr et al., 2017). Among adults with ASD, hostility – the cognitive component of anger and aggression -- is often problematic and associated with social difficulties, emotional reactivity, and poor inhibitory control (White et al., 2012).

There is also now a growing literature base **implicating impaired ER in the high rates of comorbid mood and anxiety disorders in ASD** (Mazefsky et al., 2014; Rieffe et al., 2014). Mood (depression) and anxiety disorders are particularly common, and often co-occurring, in people with ASD (Hollocks et al., 2014). In community samples, up to 80% of children meet criteria for at least one additional disorder, and these problems tend to persist from adolescence into adulthood (Gotham et al., 2015; Simonoff et al., 2008). Most children with ASD who have a comorbid psychiatric disorder continue to have at least one comorbid diagnosis into adolescence and early adulthood (Verheij et al., 2015). Over half of adults with ASD are diagnosed with at least one additional psychiatric disorder, a rate that is considerably higher than what is seen in the general population (Croen et al., 2015). One recent study found that up to 1 in 2 adults with ASD surpassed threshold

for at least one anxiety disorder (Smith et al., 2017). In a large sample of adults with ASD, three-quarters self-reported co-occurring anxiety and depressive disorder diagnoses (Gotham et al., 2015).

ER impairments may also contribute to negative social outcomes. For example, failure to manage intense negative emotion in the context of social discourse affects others' (peers, teachers) perceptions of the individual and diminishes the young person's ability to form relationships. This may lead to negative expectancies for future interactions and a cycle of social avoidance, missed social opportunities and failure to learn new social skills (Spence et al., 1999), resulting in a synergistic interaction between social impairment, ER impairment, and emotional disturbance (e.g., anxiety, depression) (White et al., 2010).

Finally, there is a growing body of research indicating that **impaired ER, psychiatric symptoms, and problem behavior are mechanistically involved in the functional impairments** experienced by young adults with ASD. Personal accounts from individuals with ASD, teachers, and caregivers identify ER impairment as a critical barrier that interferes with success in mainstream secondary classrooms (Ashburner et al., 2010). In our previous research, impaired ER was identified as a top challenge for individuals with ASD transitioning to adulthood and was associated with negative psychiatric and educational outcomes (Golt & Mazefsky, 2017; White et al., 2016). Recent research on predictors of inpatient hospitalization among children and adolescents with ASD has similarly shown that psychiatric comorbidity, and specifically presence of mood disorders, significantly increases risk of hospitalization (Righi et al., 2017), thereby playing a role in the significant health care expenditures of those with ASD across the lifespan (Hamdani & Lunsby, 2016). Indeed, young people with ASD utilize psychiatric services at much higher rates than do individuals without ASD (Croen et al., 2006).

In sum, adolescents and adults with ASD face a host of mental health, behavioral, and social challenges that do not remit as a function of development. ER impairment directly, and indirectly via problem behaviors, impacts social functioning, interferes with success in school or work, and reduces quality of life (see Figure 1). One approach to the management of emotional and behavioral concerns is psychotropic medication; at present, two antipsychotics are FDA-approved for the treatment of irritability in ASD (Marcus et al., 2008; McCracken et al., 2002). Indeed, many adolescents and adults with ASD are prescribed multiple psychotropic medications, the majority of which are associated with considerable adverse effects (Aman et al., 2015). The complexity of polypharmacy and its management, along with oftentimes unclear clinical impact and unwanted side effect profiles, makes pharmacological treatment undesirable or ineffective for many teens and adults with ASD (Nurmi et al., 2013; Saqr et al., 2017). For these reasons, it is imperative that effective psychosocial interventions also be developed to support the successful transition to adulthood, and that these interventions include an emphasis on ER, given the extent to which it interferes with functioning and outcomes.

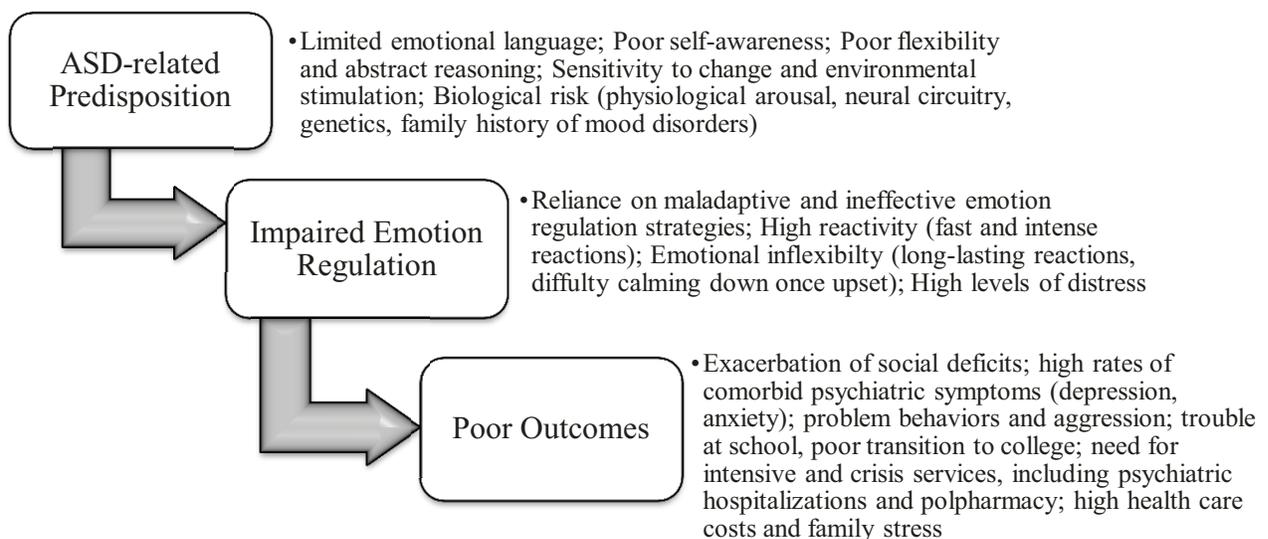


Figure 1. Illustrative summary of the propensity for impaired emotion regulation in ASD, its common manifestations, and the resultant poor outcomes (detailed in Mazefsky & White, 2014).

1E. Mindfulness training is ideally suited for improving emotion regulation in this population.

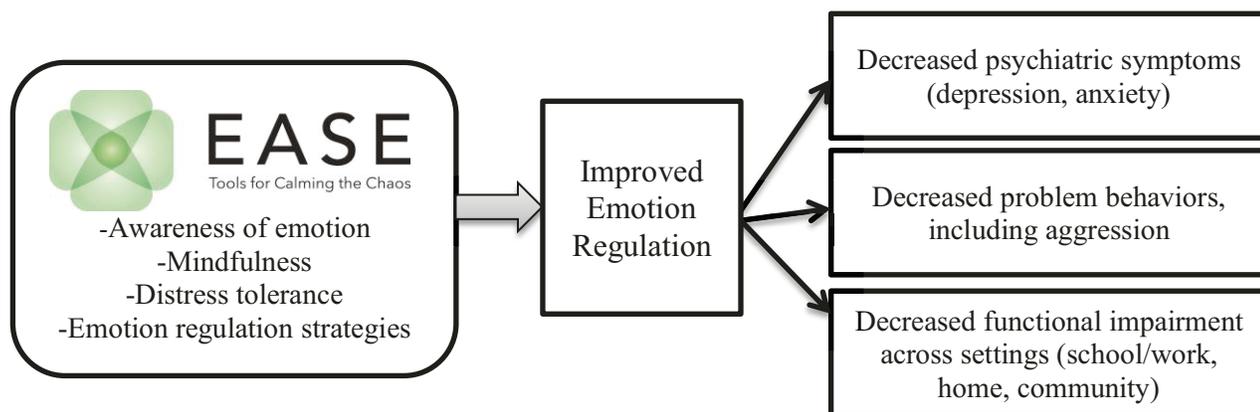
In the last 25 years, psychotherapy has seen an emergence of mindfulness-based interventions (MBI) across diverse populations (Herbert & Forman, 2011). Mindfulness is an approach that cultivates increased awareness of internal reactions and an open and accepting attitude through the use of meditative practices and activities (Baer, 2003; Kabat-Zinn et al. 1985). Mindfulness-based Stress Reduction (MBSR) and Mindfulness-based Cognitive Therapy (MBCT) are the two primary standardized mindfulness interventions that have demonstrated robust effects of improving depression, anxiety, stress, and quality of life in both clinical and nonclinical populations (Baer & Krietemeyer, 2006; Gotink et al., 2015). Researchers have also been developing interventions that utilize a mindfulness theoretical orientation or a small set of mindfulness practices but are not the MBSR or MBCT curriculum in order to specifically tailor therapy for a unique population (Chiesa, 2013; Houry et al., 2013). These approaches have been produced ER-related improvements, including inflexibility, rumination, or strengthening more adaptive approaches such as reappraisal and perspective taking (Gu et al., 2015).

Previous research provides emerging evidence to support the utility of mindfulness with adolescents and adults with ASD (e.g., Cachia et al., 2016; Conner & White, 2017). Two small open pilot studies (n=3 each) found that teaching Mindfulness in the Soles of the Feet, a mindfulness practice, to adolescent males with ASD with varied cognitive abilities was effective in reducing aggression (Singh Lancioni, Manikam, et al., 2011; Singh Lancioni, Singh et al., 2011). Spek and colleagues (2013) utilized modified MBCT treatment with 42 adults with comorbid depressive and anxiety symptoms, and results included decreases in depression and anxiety symptoms and rumination, as well as increases in positive affect. In a second study of 50 adults with ASD, reductions in anxiety, depression, somatization, sleeping problems, and rumination were observed, and increased positive affect and overall well-being were noted. Additionally, a 9-week follow-up assessment found that decreased rumination influenced anxiety levels and that intervention effects were sustained (Kiep et al., 2015). However, no study of a MBI with individuals with ASD to date has utilized randomization or a control group. Further, treatment targets were symptom-specific (e.g., aggressive behaviors, depressive and anxiety symptoms) rather than mechanistic, which is important given the promise of experimental therapeutics, which target identified mechanisms (e.g., ER) linked to clinical outcomes. Our study would be the first to use a comparison group in order to better understand how the MBI will target ER, and the first to center on adolescents and emerging adults beyond teaching a single mindfulness activity (Singh et al., 2011).

Although there are several candidate mechanisms through which MBI exerts clinical effect, there is a sizeable body of research indicating that improved ER and increased awareness are primary target mechanisms (Gu et al., 2015). Limited emotional insight and awareness is common in ASD (Griffin et al., 2016). Because awareness of one's emotions is necessary for successful ER, mindfulness may be particularly suited for treatment of ER impairments in ASD. Further, mindfulness treatment has been associated with anatomical changes in areas associated with cortical regulation and ER (Hölzel et al., 2011) and functional changes during meditation (Ives-Deliperi et al., 2011). Sustained (i.e., 4 months post-treatment) effects of mindfulness-based treatment measured via EEG have also been documented (Davidson et al., 2003).

A growing body of research also supports the efficacy of cognitive-behavioral therapy (CBT) for co-occurring anxiety in children and adolescents with ASD. However, treatment response has been variable, and preliminary evidence suggests that complex problems (e.g., episodic self-injury), may not be remediated by treatments developed for anxiety (Lickel et al., 2012; White et al., 2013). Moreover, existing treatment protocols are disorder-specific (e.g., CBT for social anxiety in ASD) and many other common problems such as explosive behavior, irritability, and depression have yet to be investigated. Additionally, high-level cognitive regulatory strategies, such as reappraisal (oft targeted in CBT), may be difficult to employ when the adolescent is in distress and dysregulated. In such cases, 'default' regulatory approaches may overwhelm the ability to use more adaptive strategies (Aldao et al., 2010). This is especially likely among adolescents, given hormonal and biological changes that influence social-affective engagement and ER in a 'bottom up' fashion (Crone & Dahl, 2012). For individuals with ASD, approaches that promote top-down regulatory strategies (e.g., thought restructuring) alone, or avoidance of environmental triggers, may be less effective than strategies to develop the client's distress tolerance, emotion acceptance, and ability to identify emotions.

Although EASE was informed by CBT, it is fundamentally distinct and emphasizes mindful awareness. Whereas traditional CBT emphasizes identifying and changing dysfunctional thoughts and emotions, EASE teaches awareness without judgment. Additionally, whereas CBT relies on problem solving as a means to decrease the experience of negative emotion, EASE emphasizes emotions as natural and unavoidable (they are not a symptom of a problem). As such, the goal of EASE is not to learn to avoid negative emotions or to change the thoughts that trigger them, but rather to develop skills which allow the individual to manage stress and act in ways that are more adaptive in the face of strong negative emotion. These strategies are often very ‘in the moment’ - such as intentionally focusing attention on a particular sensation rather than thought-based. As in CBT, the connection between thoughts and emotions is taught, but the goal of doing so in EASE is to help the client recognize the distinction between self and thought, and to ‘place the power of choice’ with the client. In other words, he might choose to re-frame an unhelpful thought to make it more adaptive, or he might decide that the thought does not need changing and, by doing so, be able to distance his emotional state from that thought. In sum, although some of the skills taught in EASE resemble concepts in CBT, the philosophical approach and emphasis differ substantially. Given preliminary evidence of [1] of MBI improving anxiety, depression, and aggression (Singh et al., 2011), [2] research supporting preliminary efficacy with adolescents (Singh et al., 2011) and adults with ASD (Conner & White, 2017; Spek et al., 2013), and [3] evidence that MBI specifically targets awareness and ER, we believe that a MBI developed for people with ASD (i.e., EASE) will likely be of high clinical import (Figure 2).



1.F. Preliminary Studies

Overview of prior research and team expertise. PI Mazefsky and the Virginia Tech Co-I White have complementary expertise as well as a long history of successful collaboration. Dr. Mazefsky is a recognized expert in ER broadly, pioneering its research in ASD. She also developed a sensitive measure validated for ASD to capture ER for treatment monitoring. Dr. White has led development and evaluation (via open and randomized trials) of several psychosocial and computerized interventions for ASD. As examples, she developed one of the earliest CBT programs for co-occurring anxiety in adolescents with ASD, which was tested in a federally funded randomized controlled trial (RCT; White et al., 2013). Recently, she completed data collection with a sample of adolescents and young adults with ASD (n = 50) who participated in an RCT to evaluate impact of a novel college transition program targeting preparedness for postsecondary education. On these projects, both PI Mazefsky and Co-I Conner were involved (White et al., 2016; White et al., 2017). Dr. Mazefsky and Dr. White also share expertise in adults with autism, and in fact co-authored the first chapter on adults with ASD ever included in the key autism resource, the 4th Edition Handbook of Autism and Pervasive Developmental Disorders (Mazefsky & White, 2014b). Dr. Beck and Dr. Conner both completed dissertations that involved open trials of mindfulness interventions for adults with ASD (e.g., Conner & White, 2017), and both have experience as clinicians in clinical trials. Dr. Minshew’s 25+ year ASD research program has informed the approach used in EASE and has included investigation of other successful interventions built off this foundation (e.g., Cognitive Enhancement Therapy for adults with autism).

ER impairments in ASD. We conducted the first study of ER in verbal adolescents with ASD, which highlighted their reliance on maladaptive ER strategies (Mazefsky et al, 2014). Further, the use of maladaptive ER strategies was associated with increased depression and anxiety, and in a later study, we also demonstrated its association with increased perseverative angry thoughts and behavioral problems (Patel et al., 2017). Using a different national sample of 1228 youth with ASD, we found that increased impaired ER was also associated with a greater likelihood of school disciplinary actions (suspensions, expulsions), psychotropic medication use, in-home crisis intervention services, police contact, and psychiatric hospitalization (Golt & Mazefsky, 2017). We also found that psychiatric inpatients with ASD have significantly greater impaired ER than community samples, further supporting ER as a significant risk factor for poor outcomes (Mazefsky et al, submitted). Using a mixed-method design including focus groups and online surveys, we found that there was consistent agreement across primary stakeholders (i.e., parents, educators/support staff from secondary and postsecondary institutions, and students with ASD) identifying ER deficits as a primary barrier to successful transition to college as well as a need for more support in this area (White et al., 2017). In a separate sample of clinically-referred children and adolescents (n= 61; age 7-17), we found that, compared to youth diagnosed with other psychiatric disorders, youth with ASD were rated as having more maladaptive ER strategy usage, less adaptive ER, and the presence of impaired ER was associated with worse set shifting abilities (regardless of emotional state) (Conner et al., in preparation).

EASE manual development and stakeholder input. With pilot funding (Edith L. Trees Charitable Trust & State of Pennsylvania) we developed the EASE treatment manual and all supporting materials (e.g., online supports), and conducted the first open pilot of the intervention. EASE is a 16-week individual therapy program for verbal adolescents and young adults with ASD, designed to improve ER capacity. EASE emphasizes awareness of one's own emotional responses as a foundational skill that promotes the ability to manage intense negative emotions, which is taught through mindfulness. Once increased emotional self-awareness is achieved, the therapist works with the client to build his/her tolerance for distress through practicing different strategies for emotion management. We used a participatory action framework to manual development, which is believed to be critical to overcoming health care disparities for people with ASD (e.g., Nicolaidis et al., 2011). After we developed the materials, we sought input from individuals with ASD, therapists experienced in MBIs, ASD, and manualized intervention trials, and parents of children with ASD. The first person who reviewed the manual is a psychiatrist who has high-functioning ASD herself. Given her unique perspective as both a clinician, who has supported adolescents and adults with ER impairment, and as a person with ASD, we made revisions based on her suggestions before inviting the other stakeholders to review.

After incorporating all stakeholder feedback, we piloted EASE with a small group (n=20) of cases at both sites (Pitt and VT), with 8 different therapists (MS and PhD level). This pilot allowed us to test implementation and preliminary efficacy, as well as to refine study procedures including therapist training and cross-site supervision, online data collection procedures, and training of the treatment naïve raters to reliability standards. In the open pilot, we conducted a feedback interview (in addition to the satisfaction ratings) at completion of each participant's involvement. In general, the parent and participant feedback was extremely supportive of EASE (see Intervention supporting file for testimonials). We also received constructive feedback about the length of the assessment battery, and pacing of the strategies taught. As a result of this three-phase process (preliminary stakeholder input and modification; open pilot study; integration of feedback from participants), we now have the final version of the EASE manual, including therapist training materials, fidelity monitoring procedures, online support (eCoach), worksheets, and a treatment protocol suitable for testing in a clinical trial.

Multi-site procedures. We refined our cross-site trial procedures, including human subject approval with IRB (Pitt # PRO16040042; VT # No. 16-129), clinical supervision, data collection, and training of therapists and masked independent evaluators. We are securing single-IRB approval, with VT ceding approval to the Pitt IRB. Additionally, we have been using the GUID (globally unique identifier) system for ID generation for participants, consistent with NIH requirements for data sharing. Using a secure video storage and transfer site, we have been conducting cross-site supervision with all clinicians on a weekly basis. Data are primarily collected online at both sites, via a secure platform housed at Pitt (WebDataXpress). Although we had some

missing data from the beginning of the trial when there were unforeseen glitches in the system, the WDX program is now running smoothly, and minimizes errors and missing data because participants enter all data directly into the system, eliminating the need to data entry that produces human errors.

Feasibility and acceptability. EASE has been piloted in a two-site, ongoing open clinical trial. Inclusion criteria included: 1) ages 12 to 17, inclusive; 2) a clinical diagnosis of ASD, confirmed by ADOS-2; 3) Verbal IQ score > 80; 4) Fluent in English; 5) Problems with ER per parent report; 6) Parent/guardian available to attend sessions. Exclusion criteria included: 1.) Serious suicidal/homicidal ideation; 2.) Past or current diagnosis of a psychotic disorder; 3.) Receiving concurrent psychotherapy treatment for emotional issues that overlaps with the current study.

Pilot data support the feasibility of recruitment (20 eligible participants enrolled within less than six months across two sites; there is now a rapidly growing waiting list for the larger trial), acceptability of EASE to consumers (based on quantitative and qualitative data and high retention rates), and viability of dissemination (high treatment fidelity across 8 therapists and 2 sites). Of the 20 participants who were eligible and enrolled in the program, two dropped out, 13 have completed the program (one of these is still completing post-treatment assessments) and 5 are ongoing with regular attendance; therefore data is available from 12 participants for preliminary analyses; of these, one had some missing pre-treatment data, and one had some missing post-treatment data, leaving 11 available for all measures except CGI. Table 1 summarizes the characteristics of the preliminary sample and the adolescent’s satisfaction ratings provided at post-treatment.

Preliminary efficacy evidence in adolescence. Pilot analyses indicate that EASE is associated with positive outcomes. Thus, far, Clinical Global Impressions-Improvement scores (made by an independent rater) that take functioning across environments and overall symptom impairment into account correspond to a mean of “Much Improved” (Mean = 2.25; SD = 0.63), with 100% of participants demonstrated at least some improvement, as determined by independently rated CGI-I. Table 1 shows the results of paired sample *t*-tests for participants who completed EASE by 9/25/17. Given the sample size available at the time, effect sizes provide better preliminary evidence of efficacy, with all but one achieving a Cohen’s *d* effect size ($d = |\text{Mean Difference}/\text{SD}|$) considered medium to large. Effect sizes on measures of ER were all medium-to-large, and functional improvement after treatment rated by an independent rater was quite large ($d = 2.81$), signifying the potential benefits of ER intervention to adaptive function. Although the EDI scores did not reach significance ($p = .06$), the effect size of EDI score was 0.74, notably higher than test- retest of EDI scores in a treatment stable sample ($n = 432, d = -0.06$). Figure 1 illustrates the mean decreases in emotional reactivity, problem behaviors/irritability, and depression from baseline, to midpoint, to endpoint. Although these data are promising, they are not definitive given the small sample size and lack of a control group.

Table 1. Demographic information and self-report treatment satisfaction for participants who completed EASE

n = 12	M/SD, Range or %/n
Age	14.7 (1.6)
Race	75% (9) Caucasian, 16.7% Asian (2), 8.3% (1) African-American
Gender	81.3% male (n = 10)
Full Scale IQ	102.8 (10.1); 83-115
Baseline CGI-Severity	4.43 (.67); 3 (mildly) to 5 (markedly) ill
How helpful was the program?*	4.25 (.87)
How much of an impact did the treatment have?*	4.08 (.90)

*On a 1 (not helpful/no impact) to 5 (very helpful/high impact) scale

Table 2. Preliminary Effect Size Estimates from Pre- to Post-EASE

Construct	Measure	<i>n</i>	Mean Difference (<i>SD</i>)	<i>d</i>	<i>t</i>	<i>p</i>
Functional Impairment	CGI-Improvement	12	-1.75 (.62)*	2.81	-9.75	<.001
Impaired ER	EDI-Reactivity theta score	11	-.49 (.67)	.73	-2.40	.037
Maladaptive ER strategies	RSQ – Involuntary engagement	11	-11.46 (4.30)	2.67	-8.84	<.001
Depression	PROMIS-Depression	11	-7.27 (8.26)	.88	-2.92	.015
Problem Behavior	ABC-Irritability	11	-5.73 (7.25)	.79	-2.62	.026
Anxiety	PROMIS-Anxiety	11	-4.46 (10.85)	.41	-0.98	.203

Note. *For CGI-I, value represents mean change from 4, which equals no improvement; Parent report data shown

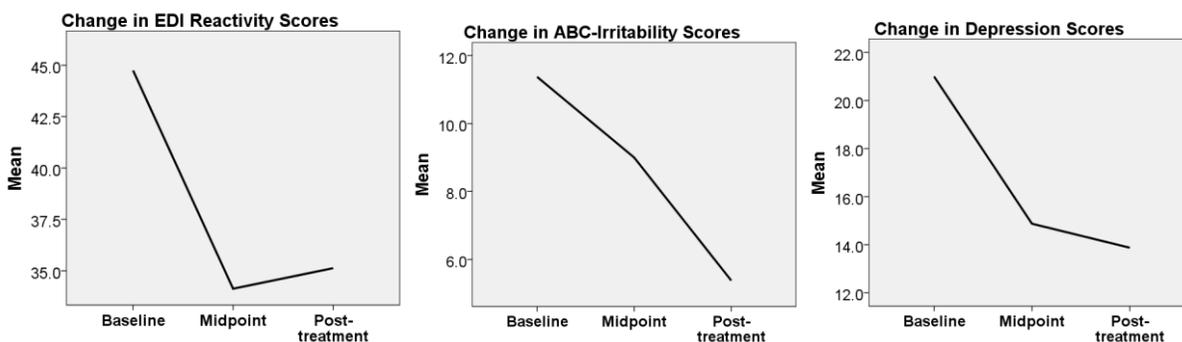


Figure 3. Illustrative examples of group mean change in key measures from baseline to post-treatment

Preliminary Efficacy evidence in young adults. Some of EASE’s content was informed by Conner & White (2017)’s ER-focused MBI open pilot that involved nine young adults with ASD age 18-25 who reported impaired ER (no cutoff on ER impairment was used). The baseline CGI-Severity scores covered the same range as the adolescent sample, though the adult sample was slightly less impaired, with a mean baseline severity (CGI-S) of 3.67 (*SD* = .71). The CGI-Improvement scores were similar to the EASE adolescent sample (2-3; *M*= 2.67; *SD*= .50). Treatment satisfaction was acceptable (*M*= 8.13; scale 1-10). In addition, seven of the nine participants had reliable improvement in impulse control, access to ER strategies, or emotional acceptance as measured on the Difficulty in Emotion Regulation Scale (Gratz & Roemer, 2004). While these results are promising, they are limited by the absence of a control group and lack of a required threshold for ER impairment to be enrolled in the study.

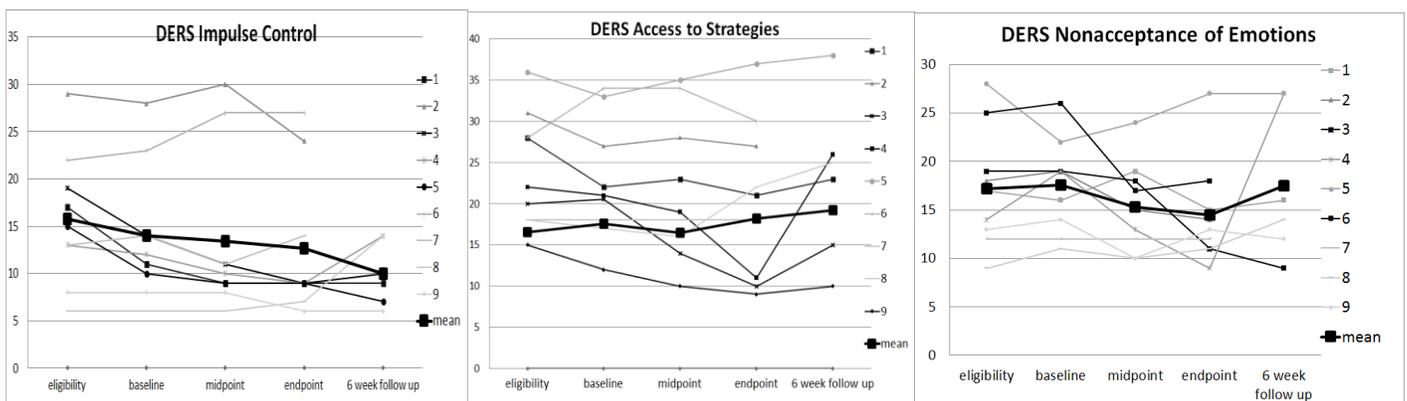


Figure 4. Individual and Mean Changes in DERS subscales

1.G. Need for Current Study and Impact

ER impairment, psychiatric symptoms, and problem behaviors exacerbate social deficits, increase distress, and interfere with the achievement of positive adult outcomes. Given that (1) outcomes tend to be poor in early adulthood for people without intellectual impairment, (2) psychiatric comorbidity is high, and (3) current psychosocial interventions are extremely limited in scope, and there is a need for an intervention that is appropriate for both adolescents and young adults with ASD that is mechanistically based. Although psychosocial interventions for ASD have burgeoned in recent years, there has been very little research aimed at remediation of the core therapeutic mechanisms of action (Lerner et al., 2012). Given evidence from multiple levels of analysis that many behavioral problems and psychiatric comorbidities in people with ASD arise from ER impairment, we have developed a psychosocial treatment specifically *targeting ER impairment via mindfulness* as the therapeutic mechanism of action. Based on our own prior research, including a two-site open trial of the program, and research by other teams, there is growing evidence that mindfulness can be targeted in ASD and that it leads to improved ability to manage intense emotion.

Potential impact of this research is substantial. EASE has the potential to impact a number of conditions that frequently co-occur with ASD, such as depression, reactive aggression/problem behavior, and anxiety. Given that the program was designed to be appropriate for adolescents and young adults, it takes a lifespan approach to promoting success during this critical, high-risk transition period. Finally, the program was developed using a participatory action approach, integrating perspectives from multiple stakeholders. This will ensure the final curriculum is maximally portable and easily disseminated once we demonstrate efficacy.

1H. AIMS

The primary objective of this study is to formally evaluate efficacy of EASE via a sufficiently powered, two-site randomized-controlled trial (RCT). Our aims are consistent with several FY17 ARP **areas of interest**; specifically, EASE: (1) is a behavioral, non-pharmacological therapy that (2) alleviates co-occurring conditions (e.g., depression, aggression, anxiety), and (3) promotes success during the transition to adulthood. This proposal is innovative in many aspects, perhaps most substantially in that it targets a theoretically and empirically based transdiagnostic process (i.e., impaired ER) during a critical transitional period during development. As such, and consistent with the spirit of the ARP Clinical Trial Award, this research is expected to have a major impact on the treatment of ASD.

A total of **80 adolescents and young adults with ASD** (age 14-21, inclusive) will be randomly assigned to either EASE or an active control condition (ACC), consisting of supportive therapy that is matched on therapist time to EASE but does not contain EASE's active ingredients (e.g., mindfulness).

Aim 1 (Primary Outcome): Show that EASE improves emotion regulation.

- ❑ H1a: Participants in the EASE group will demonstrate a steeper decline in ER impairment, relative to the ACC group.
- ❑ H1b: Participants in the EASE group will demonstrate less reliance on maladaptive ER strategies, relative to the ACC group.

Aim 2 (Secondary Outcomes): Demonstrate that EASE results in decreased functional impairment and reduced psychiatric symptoms and problem behaviors.

- ❑ H2a: Participants in the EASE group will demonstrate significantly decreased functional impairment after treatment, relative to the ACC group.
- ❑ H2b: Following treatment, participants in the EASE group will show significantly greater reductions in psychiatric symptoms and problem behaviors relative to the ACC group, including depression, aggression/problem behavior, and anxiety.

Aim 3 (Durability): Examine the trajectory of change including the degree to which effects are sustained after treatment completion.

- ❑ H3a: Participants in the EASE group will maintain significantly greater gains in ER ability, functioning, and reduced psychiatric symptoms, and at 3-months post-treatment follow-up compared to ACC group.

- ❑ H3b: ER impairment will not return to pre-treatment levels three months after treatment completion.

Aim 4 (Exploratory - Mediators): Evaluate whether changes in ER and mindfulness mediate improvements.

- ❑ H4a: Decreased ER impairment will predict decreased functional impairment and psychiatric symptoms.
- ❑ H4b: Increased mindfulness will predict decreased ER impairment.

II. Methodology

1.I.a. Experimental Intervention - EASE

Theoretical and mechanistic basis. EASE was designed to address the common ER profile in ASD, characterized by a tendency to react intensely without awareness or forethought (see Mazefsky & White, 2014a). High negative emotion and arousal, combined with poor emotional insight and self-monitoring, may result in fast emotion escalation and prevent the person from employing a healthy regulatory strategy. EASE addresses these obstacles by developing awareness of emotion at varying degrees of intensity, teaching strategies to regulate in the face of intense emotion, and practicing these skills in natural settings and applied to situations that elicit the most dysregulation for the client. In the EASE program, we provide a model for grouping strategies (see Figure 5: ABCD model), with the goal of helping the client learn that more than one strategy can be chosen, once the response is noticed in the moment (awareness). The four modules build upon one another: Awareness (building awareness of emotions and reactions), Breathe (intentionally focusing on mindful breathing before responding or judging), Change (reframing the thought or situation, or distancing self and emotion from the thought/situation), and Distract (temporarily re-focus attention to gain control).

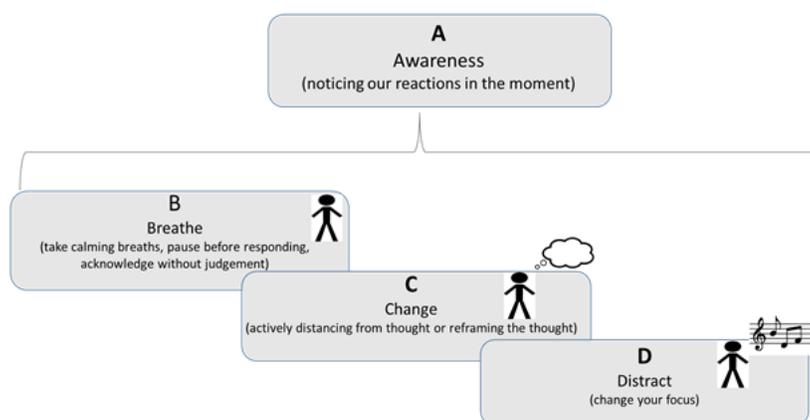


Figure 5. ABCD Model of EASE

Mindfulness is the cornerstone of EASE. It is used to improve emotion awareness and encourage decentering of body- mind (separating the links between thoughts, feelings, and self), which is taught with focused meditative practices on present-moment experiences, thoughts, emotions, and body sensations (Baer, 2000; Kabat-Zinn et al., 1985). Improving awareness of internal reactions has consistently shown to target cognitive and emotional reactivity and mediate functional improvements in clinical and nonclinical populations (Gu et al., 2015). Finally, given that ER impairment often manifests in social situations, EASE’s treatment targets are addressed within the context of the individual’s unique personal social challenges and triggers. Prior to every session the therapist identifies a social ‘challenge’ relevant for the client. Although the curriculum provides suggestions for how to practice new ER skills during the social challenges, therapists use discretion and clinical judgment to personalize this component based on the client’s *Needs Assessment* (conducted online prior to the first session, by the youth and parent, separately).

Format. The EASE program includes sixteen 50 to 60-minute sessions over 16 weeks. The treatment is delivered individually by a therapist and is supported by parent involvement and online content. Each session begins with a mindful check-in, review of prior material, and agenda setting, then proceeds to skill teaching and practice, practice of a mindfulness exercise, and planning for post-session practice. EASE includes community sessions, which often occur outside of the clinic, in situations that are both challenging and relevant to the client’s daily life. This provides an opportunity to practice skills in a more natural environment, reinforce learning, and improve generalization. Both the client and parent also have access to emotionCoach (i.e., “eCoach”), the online platform for EASE that includes all of the intervention materials, audio recordings of mindfulness exercises, and additional tips and information. Having materials from session and information to

support the concepts introduced in session available online allows clients to learn and process information at their own pace and aids in synchronous learning for parents.

Use of **an individual therapy approach** permits flexibility in the delivery of the treatment and promotes dissemination in clinical settings where groups may not be practical. Based upon our pilot study, participants differed greatly in their presentation of impaired ER, likely ER triggers, and response to specific mindfulness strategies. An individual therapy modality allows the clinician to devote time to mindfulness practices that are especially challenging for the participant, and base other activities around the participant’s specific difficulties. We also found that the community sessions were instrumental in generalizing new skills, and these sessions would be limited logistically with a group modality. The goal of the community sessions in EASE is not to simply practice ER in social situations (as one might be able to achieve in a group format), but rather to apply the newly learned ER skills in settings and situations that most closely mimic the specific context where the participant experiences the most dysregulation. Further, the individual therapy format facilitates personalization to accommodate the person’s circumstances, which vary significantly in this age range (e.g., in school or working, living with parents or alone). Finally, we considered a predominantly individual therapy approach, supplemented by some group sessions. However, Co-I White has prior experience with this structure, experiencing numerous logistical barriers; further, such a structure would be a difficult model to translate into clinical practice.

1.I.b. Control Intervention – Supportive Therapy

Although we considered an inactive control condition, such as a wait-list group, we opted for a more scientifically rigorous design for 3 reasons. First, use of an active control condition (ACC), will allow us to test the efficacy of the ‘active’ ingredients of EASE (i.e., mindfulness, emotion awareness, ER strategies). Second, with the inactive control, we would not be able to rule out the effect of factors such as the therapeutic relationship and familial expectation of treatment benefit. Third, use of the active comparator allows for a more rigorous test of effect via independent, assignment-naive (‘blinded’) evaluators. The ACC will involve non-directive, supportive psychotherapy and education, which is a well-established ACC, often used in RCTs involving youth (e.g., Piacentini et al., 2010) and in trials evaluating MBIs (e.g., Shallcross et al., 2015). We structured the ACC based on guidelines set forth by clinical trial methodologists (e.g., Baskin et al., 2003; Kazdin et al., 1990). The ACC is *structurally equivalent* to the experimental intervention in that it is implemented by the same therapists, over 16 50- to 60- minute sessions, in an individual format. Additionally, the purported *active ingredients* of EASE are expressly contraindicated in the ACC. In the ACC, the clients and parents will be allowed to discuss any topics and stressors with the therapist, but the therapist is prohibited from providing mindfulness training.

1.I.c. Overview. We propose to conduct a sufficiently powered RCT of EASE, across two clinical sites. The design and participant flow is depicted in Figure 6.

1.I.d. Sample and Ascertainment

Sample. A sample of n = 80 male and female adolescents and young adults with ASD will be enrolled. The expected male to female ratio is 4:1, based on current prevalence estimates of diagnosed ASD. With a conservative estimate of 25% attrition, we would achieve a final sample size of 60. Pitt will enroll 50 participants, and VT will enroll 30 (due to budget restrictions and population access).

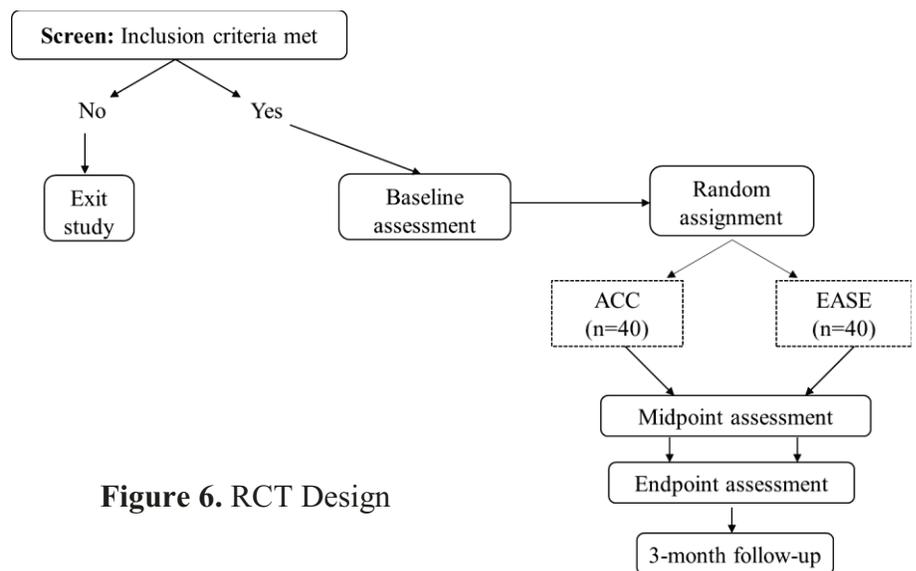


Figure 6. RCT Design

Inclusion criteria consist of: (1) an ASD diagnosis, based on expert clinical opinion and supported by ADOS-2; (2) age 14-21 years; (3) Verbal IQ \geq 80; (4) fluency in English; (5) a parent available and willing to participate; (6) evidence of at least an average degree of ER impairment for ASD (T-score of 45 or higher or 0.5 SD below the mean; on the Emotion Dysregulation Inventory Reactivity Short Form); and (7) medications are permitted but must be stable for 4 weeks with no planned changes.

Exclusion criteria consist of: (1) Current suicidality or homicidality that warrants more immediate care; (2) active psychosis; (3) Receiving concurrent psychotherapy treatment for emotional issues (i.e., depression, anxiety, anger) that overlaps with the current study.

Recruitment. This study will take place at: The University of Pittsburgh (Pitt.) in Pittsburgh, PA and Virginia Tech (VT) in Blacksburg, VA. Pitt Sample. Dr. Mazefsky is associated with the Center for Excellence in Autism Research which has been running studies with verbal individuals with ASD for 30+ years. Dr. Mazefsky recently completed two studies with adolescents (10-17 and 12-19) with ASD. In an assessment-focused study, 30 adolescents were recruited within less than 2 years. In an fMRI study, 26 adolescents with ASD were enrolled within 1 year. Dr. Mazefsky also leads a study on the ASD specialized psychiatric inpatient unit at Western Psychiatric Institute and Clinic, where the reason for admission is typically emotional and behavioral dysregulation; this will be an ongoing source of recruitment (upon discharge). Finally, Dr. Mazefsky has established collaborations and recruitment strategies in place with the Pittsburgh Autism Treatment Network and a high-volume outpatient clinical for ASD. VT Sample. In a recently completed RCT with adolescents with ASD, over a 24-month recruitment period, 36 potential participants were screened for eligibility (which was more stringent than current study), of whom 83% ($n = 30$) met study criteria and were randomized. In two separate funded treatment trials currently underway, Dr. White is enrolling (on average) 2 adolescents and 2 adults per month. The clinic where this study will take place is well-recognized in the community, with a waiting list for treatment and registries carried over from prior studies. Additionally, Dr. White is a stakeholder and affiliate of the VT Center for Autism Research, a large-scale participant registry of children and adults with ASD interested in treatment research.

Eligibility determination and sample characterization will begin by phone, following verbal consent to screen. Phone screening will include a brief interview about the inclusion and exclusion criteria, including the 7-item EDI Reactivity Short Form. If participants pass the phone screen, they will complete an in-person informed consent/assent and assessment to confirm their ASD diagnosis and ensure that their Verbal IQ \geq 80.

Randomization. Participants will be randomly assigned to EASE or ACC once eligibility is confirmed, by a data manager independent from the PIs and clinical team. Randomization algorithms have been created by the study statistician, independent of the PIs. Randomization will be done to ensure equal numbers of EASE and ACC at each site. Group assignment will be communicated to the PIs and assigned study clinician, who will then inform the participant. Site PI's (Mazefsky and White) will closely monitor screening and randomization procedures and, should difficulties (e.g., more withdrawals from ACC than active) arise, they will be addressed immediately with the Data Safety and Monitoring Board.

Therapist training: At the start of the RCT, all therapists will convene for a training meeting for both treatments, on site at Pitt. The PIs will provide the theoretical background and didactic training, including live and video (from open pilot) demonstration of specific strategies. Study therapists must observe each recorded session (from open trial) before delivering that session with a study participant. In addition, every session of the first case of every therapist will be observed for integrity and training purposes by the respective site PI.

'Blind' maintenance: All Independent Evaluators will be 'blind,' or naive, to treatment assignment, and they will instruct participants not to reveal what intervention that they are receiving during the course of the procedures. Meetings with the independent raters will be conducted in a different office than the therapy, and the therapists and PI's will not be involved in outcome assessment. Regular assessments of treatment naive status will be conducted by the PI. When questions arise about possible need to break the blind (e.g., a potentially serious event becomes apparent during an assessment, but evaluator is not aware of treatment condition), Dr. Minshew (Co-I at Pitt) will be the first contact. She will work with the PI's to determine how to proceed. If a participant breaks the blind, we will get another rater.

1.1.e. Study Variables and Measurement

A multi-method, multi-informant assessment battery (see Table 2) will be used to provide accurate sample characterization and examine change. All measures have well-established psychometric properties for the full age range of our sample and have been used with ASD samples. We are employing **four primary reporters**: self, parent, other (e.g., teacher, co-worker), and assignment-blind clinical rater, and **four modalities of assessment**: direct testing, observational, questionnaire, and interview. Assessments will be completed at pre-treatment (baseline), midpoint (8 weeks), post-treatment (16 weeks), and follow-up (3 months after post-treatment), in addition to the primary measure of ER completed weekly by parents.

Characterization:

ASD and IQ inclusion criteria will be confirmed by: (1) the Autism Diagnostic Observation Schedule – Second Edition (ADOS-2), a semi-structured, standardized assessment that elicits behaviors relevant to the diagnosis of ASD administered by a research reliable ADOS tester (Lord et al. 2012), and (2) the Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-2; Wechsler et al., 2011), a reliable and valid measure of intelligence based on four subtests provide a brief, general estimate of functioning and a verbal IQ.

Measures with well-established psychometrics in ASD will be administered to quantify characteristics that may be related to ER and treatment response, including: (1): A subset from the Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001) executive functioning battery including the Sorting task, which assesses conceptual reasoning and problem-solving, and the Color-Word Interference task, which assesses inhibitory control; (2) The 12-item Intolerance of Uncertainty Scale (IUS-12) which measures inhibitory and prospective anxiety (Boulter et al., 2014; Maisel et al., 2016); (3) The Social Responsiveness Scale, 2nd Edition (SRS-2) as a measure of ASD symptom severity, including specific subscales designed to assess treatment effects (Constantino et al., 2004; Constantino & Gruber, 2012); and (4) a well-validated and non-invasive self-report measure of puberty, the Pubertal Development Scale (PDS; Carskadon & Acebo, 1993).

Prior to treatment, caregivers and participants with ASD will separately complete a Needs Assessment, which was developed specifically for EASE to inform case conceptualization. It is a 19-item questionnaire that asked the rater to provide ratings of difficulty, on a 1-10 scale, for situations related to ER and socialization, as well as qualitative descriptions for any relevant items.

Information on Medications and Other Treatments will collected at each time point by parent report. We gather medication data by medication class. The parent report form also gathers information about non-pharmacological treatments (e.g., social skills training) by answering yes or not to a common list of interventions as well as an option to add open-ended additional information. Information is gathered on any changes in the past 4 weeks for all medications and psychosocial interventions endorsed.

Primary Outcome (Emotion Regulation) Measures:

We have two measures of our primary outcome: (1) The EDI, which measures impaired ER, collected weekly parent report (short form), other reporter at pre-, post- and follow-up, and blind rater interview of the participant at pre-, post- and follow-up; and (2) The RSQ self- and parent report as a measure of ER strategies, collected at pre-, mid- and post-treatment, and 3-month follow-up.

Emotion Dysregulation Inventory (EDI; Mazefsky et al., 2016). The EDI was developed to assess the full range of ER impairment observed in ASD. The item pool was created with feedback from parents of youth and young adults with ASD and input from a panel of experts in measure development and ER in ASD. Next, caregivers of 1,755 youth with ASD completed 66 candidate EDI items, and the final 30 were selected based on factor analysis and item response theory (IRT) analyses. The EDI has two scales: 1) *Reactivity*, characterized by intense, rapidly escalating, sustained and poorly regulated negative emotional reactions, and 2) *Dysphoria*, characterized by minimal positive affect and motivation, and the presence of nervousness and sadness. A 7-item Reactivity short form was developed via simulated computerized adaptive testing, which is correlated .98 with the full scale. Validity evidence was supported by expected group differences (higher scores in an ASD

psychiatric inpatient versus community sample), expected correlations with measures of related constructs, and demonstration of change sensitivity. Co-calibration with legacy measures demonstrated that the EDI provides substantially more information on individual variability in ER; Figure 7 shows these test information curves for the full EDI Reactivity scale, the 7-item EDI short form, the ABC-I (15 items), an emotion dysregulation index from the CBCL (Sampson et al., 2014), and CBCL Stress Problems Scale. In a sample of 432 youth with ASD with stable treatments, paired samples t-tests across a 4-week period yielded a very small effect size (-0.06), which will be helpful in judging the meaning of EDI effect sizes for EASE.

Response to Stress Questionnaire, Social Stress Version (RSQ; Connor-Smith et al., 2000) is a 57-item self- and parent-report questionnaire of ER strategies. The RSQ asks the respondent to identify social stressors that they have experienced and then rate the questions related to these specific stressors, thereby making it more concrete and relevant to the lives of adolescents young adults with ASD. The RSQ has been shown to be valid and reliable in ASD samples (Mazefsky et al., 2014; Khor et al., 2014). The RSQ will be used to explore the change in reliance upon maladaptive strategies (i.e., involuntary engagement and involuntary disengagement).

Secondary Outcome Measures.

Functional/Adaptive Outcome Measures: Our secondary functional outcome measures include: (1) The CGI, and (2) the CAFAS, both completed by a blind rater at pre- and post-treatment, and follow-up.

Clinical Global Impression (CGI; Guy, 1976). The CGI is comprised of 2 scales: Severity (CGI-S) and Improvement (CGI-I), each rated on a 7-point scale. The CGI-I scale was designed to measure overall symptomatic change as compared to baseline. Scores range from 1 (Very Much Improved) to 4 (Unchanged) to 7 (Very Much Worse). The CGI-I has been used in many studies over the past 3 decades, including clinical trials of treatments for ASD (e.g., RUPP, 2002). In this study, the CGI-I is used as a categorical (responder vs. non-responder) outcome measure, and will assess global functioning (including functioning in school, activities of daily living, social activities, and home). In our open trial to pilot EASE, we successfully trained three independent raters to reliably assign CGI scores and established inter-rater agreement as well, cross-site.

Child and Adolescent Functional Assessment (CAFAS; Hodges, 2000). The CAFAS evaluates level of impairment in day-to-day functioning. It has over 20 years of research to support its sensitivity to change and has been applied in child welfare, juvenile justice, mental health, and school systems to identify level of functioning and needs. CAFAS domains include: School, Home, Community, Behavior Towards Others, Moods/emotions, Self Harm, Substance Use, and Thinking (assessing irrational thinking). The CAFAS has been widely used, including with samples that involved children with ASD (e.g., Bishop-Fitzpatrick et al., 2015).

Psychiatric Symptoms/Problem Behavior: Our primary measure of psychiatric symptoms and problem behavior will be the BPRS completed by a blind rater at pre, post-, and follow-up time points. In addition, we have several parent, self, and other reporter questionnaires of specific symptoms and problem behaviors that will be completed to allow tests of convergence across multiple reporters as well as to provide the possibility to evaluate composites via structural equation modeling, depending on the primary results.

Brief Psychiatric Rating Scale, Version 4.0 (BPRS; Ventura et al., 1993). The BPRS is an interview-based measure of psychopathology severity that has been widely used in clinical trials administered by treatment naive raters (e.g., Zanello et al., 2013). It has been previously used in an RCT of Cognitive Enhancement Therapy for ASD and was responsive to change (Eack et al., 2013). It has 24 items assessing

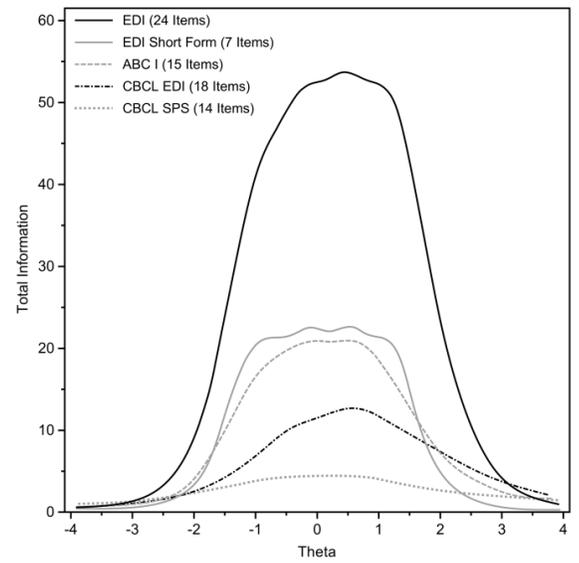


Figure 7. Test information comparison of EDI to other measures

severity of psychiatric symptoms on a scale from 1 (not present) to 7 (extremely severe) that are rated after administration of structured probes.

Aberrant Behavior Checklist (ABC; Aman et al., 1985). The ABC is a 59-item questionnaire with 5 subscales: Irritability (ABC-I), Social withdrawal (ABC-S), Stereotypic behavior, Hyperactivity/noncompliance, and Inappropriate Speech. ABC-I measures tantrums, aggression, and self-injury, and has been utilized in ASD treatment and medication studies (Aman, 2012). However, a confirmatory factor analysis of the ABC found the highest corresponding items for the Irritability subscale were self-injury and aggression items rather than items referencing tantrums (Kaat et al., 2014). Thus, the proposed study will use the ABC-I as a measure of problem behaviors more broadly. In a recent review of 38 measures of social communication concluded that the ABC-S, an index of social interaction and isolation, has the most data to support its use in clinical trials in ASD as a change-sensitive measure of social functioning (Anagnostou et al., 2015).

Measures of psychiatric symptoms will include: (1) The PROMIS Anxiety and Depression Scales (Irwin et al., 2010), which were developed via the NIH Patient-Reported Outcomes Measurement Information Systems (PROMIS) initiative as brief change-sensitive outcome measures; they were responsive to change in our open trial; (2). Five complementary forms from the Achenbach System of Empirically Based Assessment (ASEBA; Achenbach & Rescorla, 2001), including the: ABCL: other/parent-report on adult; ASR: adult self-report; CBCL: parent-report; YSR: self-report; TRF: other/teacher report). The ASEBA forms are co-normed, allowing us to examine convergence and discrepancy across reporters. The ASEBA yield t-scores for internalizing and externalizing behavior problems, as well as a range of syndrome scales (e.g., aggression, depression). The ASEBA has been widely used, including in ASD samples (e.g., Stratis & Lecavalier, 2017).

Mindfulness and Acceptance

The two measures of mindfulness and distress tolerance include: (1) The 10-item Child and Adolescent Mindfulness Measure (CAMM; Greco et al., 2011), which has adequate reliability and is predictive of favorable outcomes (e.g., grades). Co-I Beck recently evaluated the CAMM with a sample of 19-32 year old adults with ASD. Cognitive interviews and reliability analyses indicated that the CAMM was well understood and demonstrates acceptable internal consistency ($\alpha = .831$) and excellent test-retest reliability ($ICC_2 = .956$) with an adult ASD sample (Beck, 2017); (2) The Brief Experiential Avoidance Questionnaire (BEAQ; Gamez et al., 2014) is a 15-item version of the 62-item Multidimensional Experiential Avoidance Questionnaire (MEAQ; Gamez et al., 2011). The BEAQ has good internal consistency and strong convergence with the MEAQ.

Treatment and Assessment Fidelity

Participants will complete a Treatment Satisfaction Scale to obtain their impressions of the overall impact of the interventions. After each session, the clinician will complete a Fidelity Rating form that assesses client homework completion, session rapport, client involvement, and adherence to the manual. There are separate fidelity forms for EASE and ACC, with the checklist for EASE emphasizing key ingredients to cover, and the ACC checklist confirming that prohibited strategies were not introduced. At least 20% of the sessions will be observed and independently coded by two raters to ensure fidelity agreement. Finally, the Site PIs will watch occasional sessions in entirety for fidelity to prevent drift, and for supervision purposes.

Parent Self-Report Measures.

Given variability in parental functioning and the potential for parental influences on outcome, we will obtain brief parental ratings. We will repeat these at post-treatment, to enable future explorations of any potential benefits experienced by the parents themselves. Measures will include the: (1) Parenting Stress Index, Fourth Edition- Short Form (PSI-4; Abidin, 2012), a 36 item self-report questionnaire of parenting stress that contains Parental Distress, Parent-Child Dysfunctional Interaction, and Difficult Child subscales; the PSI has been utilized extensively in ASD research, including above the traditional age cutoff of 12 years (Pedersen et al., 2016; Simonoff et al., 2012); (2) The State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983), a 40-item self-report questionnaire that assesses trait and state, or current, anxiety symptoms; and (3) the BEAQ, as described above.

Table 2. Schedule of Measure Administration

Measure	Each Visit	Eligibility	Pre-Trmt	Midpoint	Post-Trmt	Follow-up
CHARACTERIZATION						
Demographics						
Autism Diag. Obs. Schedule-2						
Wechsler Abbrev. Scale of Intell-2						
Delis-Kaplan Executive Functioning System						
Intolerance of Uncertainty Scale						
Social Responsiveness Scale-2						
Pubertal Development Scale						
Needs assessment			 			
Medications/Treatments						
EMOTION REGULATION						
Emotion Dysregulation Inventory			 		  	  
Response to Social Stress Quest.			 	 	 	 
FUNCTIONAL/ADAPTIVE OUTCOME MEASURES						
Clinical Global Impressions						
Child & Adolescent Functional Assessment						
PSYCHIATRIC SYMPTOMS AND PROBLEM BEHAVIOR						
Brief Psychiatric Rating Scale						
Achenbach System: CBCL/YSR; ABCL/ASR; TRF			  	 	  	  
Aberrant Behavior Checklist			 		 	 
PROMIS Anxiety			 	 	 	 
PROMIS Depression			 	 	 	 
MINDFULNESS / ACCEPTANCE						
Brief Experiential Avoidance Questionnaire						
Child & Adol. Mindfulness Measure						
FEASIBILITY						
Treatment Satisfaction					 	
Treatment Fidelity						
PARENT SELF-REPORT MEASURES						
Parenting Stress Index SF						
Brief Experiential Avoidance Questionnaire						
State Trait Anxiety Inventory						

-  Clinician with participant (e.g., performance based, interview, or direct observation)
-  Parent-report
-  Self-report
-  Other-report
-  Assignment naïve rater
-  Clinician rating

1.J.a. STATISTICAL PLAN AND DATA ANALYSIS

Justification of sample size that is necessary to achieve the desired power

We will enroll 80 subjects at two sites. Using small-scale pilot pre-post repeated measures data ($n = 12$), we estimated the sample size to achieve the power of 0.80 for testing each hypothesis stated in the Aims 1 and 2 above from the EASE open trial. For the hypotheses to provide evidence that EASE has a differential treatment effect on ER, functional impairment, psychiatric symptoms, and problem behaviors (hypotheses 1a, 1b, 2a, 2b), Cohen's d , or standardized mean difference, ranged from small-to-medium effect size (0.41 for Anxiety) to very large (2.81 for CGI-I). The necessary sample size to detect the smallest effect size was computed as a total of 49 (per group), with a range of 4 to 28 per group for all other outcomes with larger effect sizes, and an average across measures of 17 per group. Our primary interest is in effects with at least moderate effect sizes, as they are likely to have the most real-world impact. As such, even if there was significant attrition, we should have ample power to detect the most meaningful outcomes for Aim 1 and Aim 2. To test the mediation effects (Exploratory Aim 4), we obtained the required sample size using the methodology proposed by Judd et al. (2001) and elaborated by Montoya & Hayes (2017). A necessary condition to detect mediation is that the change score for a mediator needs to be statistically significantly associated with the change score in dependent variable after controlling for the average level of the mediator. Using this framework, we found that the necessary total sample size to detect the mediation effect with power of .80 ranged from 43 to 86 (per group), where the effect size as a partial correlation in multiple linear regression ranged from large (0.44, path: Treatment \rightarrow CAMM Mindfulness \rightarrow RSQ Involuntary Disengagement) to medium (0.31, path: Treatment \rightarrow EDI reactivity \rightarrow Depression). The maximum sample size that we can feasibility ascertain for this project is 80, which gives us a chance to detect mediation processes that have large effects; accordingly, this aim is considered exploratory.

General analytic approach. Data will be analyzed based on CONSORT recommendations using intent-to-treat analyses with all participants who receive any exposure to their respective treatment condition. General linear models (analysis of variance [ANOVA] mixed models) will evaluate the differential trajectories of change between participants treated with EASE and ACC, after adjusting for demographic, medication, and other treatment confounders. It is *hypothesized* that participants who receive EASE will demonstrate significant differential improvements in ER, psychiatric symptoms, problem behavior, and functional impairments compared to the ACC. In addition, it is *hypothesized* that participants who receive EASE will maintain their gains at 3 months post-treatment compared to those treated with ACC. Exploratory analyses will also examine whether ER and mindfulness serve as mechanisms of change using a mediator analytic framework.

Because our population of interest is, by definition, vulnerable and their symptoms rapidly fluctuating, we believe it is insufficient to employ a traditional pre-post design for determination of treatment impact. For instance, a client might be responding well to treatment but then face the start of the school year immediately before the last session and experience heightened dysregulation; an analytic design that does not consider this will yield results that do not fully capture the pattern of growth. As such, we have refined our data collection procedures to include assessment of ER data at every session, which allows us to track our theorized mechanism of change in a nuanced way. We have also considered this issue in our analytic plan. After first utilizing traditional mixed model group comparisons of change, a more sophisticated analysis will be conducted using hierarchical linear models (HLM), which is also known as multilevel growth modeling (Raudenbush & Bryk, 2002). HLM casts the changes as the growth trajectories over time and allows us to examine the average amount of change, the amount of individual differences, and the correlates of changes between groups.

Medication effects. While randomization procedures should ensure comparable medication usage between treatment groups, given the modest sample size, differences in medication usage will be explicitly examined between treatment groups, and statistically controlled for in efficacy analyses if necessary.

Intent to Treat Analyses and Approach to Missing Data. Automated systems are in place via our online data collection (piloted during our open trial) to minimize occurrence of missing data. Nonetheless, intent-to-treat analyses of treatment effects will include all 80 individuals, regardless of attrition or infidelity to treatments. Both of our analytic approaches allow for missing data. ANOVA mixed models do not require that subjects be

excluded from the analyses because of a single missing data point. Multilevel growth models can also make an efficient estimation by utilizing all the available data, and further, the estimates are valid (i.e., asymptotically unbiased) when missingness occurs at random (MAR) (Little & Schenker, 1995). Even when MAR is not satisfied, the robustness of the results is maximized when all available data are used in the analysis (Schafer, 1997). In order to accommodate the case of missing ‘not at random,’ we plan to conduct a sensitivity analysis to see how much our inferences would be altered using a pattern-mixture model (Hedeker & Gibbons, 2006).

Controlling Experimental-Wise Type I Error Rates. The conduct of multiple tests of statistical inference can artificially increase Type I error rates. Several approaches will be used to control the experimental-wise error rate in this trial. First, analyses conducted to test the hypotheses of Aims 1 through 3 will be given priority over exploratory analyses conducted as part of Aim 4. Since these hypotheses about efficacy and durability of the proposed EASE program on ER and functional impairment have confirmatory nature from our prior studies and are the main hypotheses in this clinical trial, we will employ Hochberg’s correction (Hochberg, 1988) to control the experimental-wise error rate by adjusting p-values for multiple hypothesis tests in order to rigorously examine the treatment efficacy and durability. Second, in order to address the hypotheses in Aim 4, outcome measures will initially be aggregated into four multivariate composite domains (i.e., ER, functional impairment, psychiatric symptoms, and problem behaviors) based on internal consistency analyses and previous studies, which will reduce the number of hypothesis tests initially conducted. Then, exploratory analyses will be conducted for individual measures within these composite domains only if the overall multivariate composite demonstrates a significant mediation effect.

Statistical Analyses by Aim

Aim 1 (Primary Outcome): Show that EASE improves emotion regulation.

First, to test the main effects of EASE on impaired ER (Hyp 1a) and maladaptive ER strategy use (Hyp 1b), we will employ linear mixed-effects models, with an auto-regressive error structure most appropriate to longitudinal data, allowing model intercepts and longitudinal trajectories to vary across subjects. Significant treatment by time interactions showing differences in linear rates of change in EDI Reactivity (Hyp 1a) and RSQ Involuntary and Voluntary Engagement scores (Hyp 1b) will be the effects of interest in these models. All mixed-effects models will control for potential demographic and medication confounds by including age, gender, IQ, and medication information as model covariates. This will be followed by modeling of growth trajectories between groups via HLM, also controlling for relevant potential confounds, using weekly data for Hyp 1a (EDI), and pre, mid, and post-treatment data for Hyp 1b (RSQ).

Aim 2 (Secondary Outcomes): Demonstrate that EASE results in decreased functional impairment and reduced psychiatric symptoms and problem behaviors.

The test of secondary outcomes will mirror the approach used in Aim 1. To evaluate change in functional impairment via CGI-I (Hyp 2a), we will create a dichotomous variable of responder = 1 and non-responder = 0. This is consistent with convention for use of the CGI-I in both psychosocial and drug treatment studies, such that 1 and 2 codes (‘very much’ and ‘much improved’, respectively) are considered responders and all others are non-responders. The other primary outcome of interest for Hyp 2b will be CAFAS scores. For Hyp 2b (psychiatric symptoms and problem behaviors), we will focus first on the BPRS as this is our most stringent and ‘blinded’ test, followed by ABC-I and PROMIS depression and anxiety.

Aim 3: Examine the trajectory of change including the degree to which effects are sustained after treatment completion.

The goal of Aim 3 is to test whether treatment effects persist over time even after the treatment ended, and to ensure they do not return to pre-treatment levels. The hypotheses in Aim 3, similar to the hypotheses in Aims 1 and 2, will be tested with linear mixed-effects models to determine whether the differential treatment effects are maintained once the 3-month follow-up time point is included (Hyp 3a). In addition, we will utilize HLM to evaluate the sustaining effects after the intervention (Aim 3) by estimating the differential trajectories of change between patients treated with EASE and ACC controls, with an emphasis for Hyp 3b on demonstrating sustained improvements over baseline.

Aim 4 (Exploratory): Evaluate whether changes in ER and mindfulness mediate improvements.

The first step to testing mediation is to assess change in the proposed mediators. Aim 1 analyses address this for ER (Hyp 4a). This procedure will be repeated to see if CAMM scores changed over the duration of the intervention using three waves of data (pre/mid/post measurements) (Hyp 4b). Then, mediator frameworks for clinical trials will be used to assess the degree to which changes serve as mechanisms for EASE effects (Hayes, 2014; Barron & Kenny, 1986). Cast in a path-analysis model, mediation hypothesis will be examined using Mplus software package (Muthén & Muthén, 1998–2012). Considering the fact that the sampling distribution of the indirect effect, represented as the product of two path coefficients, is likely to have a non-normal skewed distribution (MacKinnon et al., 2007; MacKinnon et al., 2002), the inference on the indirect effects will be made based on the bootstrap method which is available in Mplus software package. Considering the nature of Aim 4, which is exploratory and the possibility of many paths, we will employ the following strategy to control the experimental-wise Type I error rate. First, outcome measures will initially be aggregated into four multivariate composite domains (i.e., ER, functional impairment, psychiatric symptoms, and problem behaviors) based on internal consistency analyses and previous studies, which will significantly reduce the number of hypothesis tests initially conducted. Then, exploratory analyses will be conducted for individual measures within these composite domains only if the overall multivariate composite demonstrates a significant mediation effect. All mediation analyses will control for confounds as covariates.

1.K.a. Potential Challenges, Alternative Strategies, and Design Considerations

What if EASE does not work? Although our preliminary data suggest that EASE will have a positive impact, it is possible that this RCT with a larger sample will not yield consistent results. Even if there is not evidence for the efficacy of EASE, results will inform our understanding, and treatment, of ER-related problems in ASD. It is possible, for instance, that mindfulness improves but not ER in measurable ways. It is also conceivable that ER moves but that this change is not reflected in symptomatic improvement. This study is designed such that, even if unsuccessful, the results will inform subsequent treatment research in this area.

How will we handle use of other treatments? EASE takes about 16 weeks to complete from start to finish (plus the 3-month follow-up). Based on our pilot studies and prior clinical work, we anticipate most participants will be involved in other treatments. We will not enroll participants who are actively engaged in treatment that targets ER; however, treatments such as speech therapy and family counseling will be permitted. Pharmacological treatment is permitted as well. Given prior research and the sample in our pilot study, we anticipate the majority of this sample will be medicated, and medication changes (e.g., altered dosages) are common, even though inclusion requires medication to be consistent at enrollment without planned changes. We will collect data on other treatments and changes in medication so that we can subsequently determine if this is associated with response.

Why a high-functioning sample? We deliberated on the minimum level of cognitive and verbal ability necessary for participation in this treatment, and have determined that the program is likely to be most accessible to people who do not have co-occurring intellectual disability (ID) and are verbally communicative; as such we have restricted eligibility with regard to verbal ability. Additionally, there are unique risks faced by people without ID during transition to adulthood (Taylor & Mailick, 2014), and emotional problems and high negative affect are most pronounced among higher functioning adolescents with ASD, compared to lower functioning peers (e.g., Sukhodolsky et al., 2008).

Why a 2-site study rather than single site? There is a major research to practice gap in our field; indeed, on average there is a lag of about 10 years before interventions that are research-supported are well-disseminated in clinical practice. The conduct of multi-site trials should help decrease the gap, as it requires development of manuals that can be adopted across sites, and therapist training materials. Second, Mazefsky and White offer complementary expertise to this study – Mazefsky is an expert on assessment and presentation of ER impairment in ASD, while White has expertise in treatment development, RCT design, and clinical evaluation in ASD. Third and finally, the two-site approach will permit ascertainment of a large and diverse (in terms of both ethnicity and SES) sample.

Why not use ecological momentary assessment (EMA) or other biological measures? We considered EMA to measure ER in the natural environment; however, difficulties in EMA adherence and time commitment

were seen in Conner & White’s open pilot trial MBI with young adults with ASD. Responses to text message alerts concerning current emotion ratings (randomized to 2-3 times a week) in the sample ranged from 0-100% (n=9). We considered neuroimaging, but opted to first emphasize real-world, behavioral and functional outcomes. Finally, while we would like to explore physiological arousal in future studies, it is not an ideal starting point given inconsistencies in the association between physiological measures and stress response in ASD. We have a collaborator in the Dept. of Engineering at the University of Pittsburgh (Dr. Murat Akcakaya) who is an expert in EEG and machine learning, and we are currently designing paradigms that would be ideal for pre- and post-EEG in this context. Should this proposal be funded, we hope to utilize additional resources to add EEG to our assessment battery with Dr. Akcakaya overseeing data collection and analysis.

1.L.a. Timeline

Figure 8. Study Timeline

Tasks	Year 1			Year 2			Year 3			Year 4		
DOD regulatory review	█											
Therapist training (cross-site)	█											
Dual site QA checks (data management, supervision, fidelity)	█											
Pitt participant recruitment (n = 50)*			6 4	6 4 4	6 4 4	6 4 4	4 4 4	4 4 4				
VT participant recruitment (n = 30)*			4 2 2	4 2 2	4 2 2	4 2 2	4 2 2	4 2 2				
Screening and randomization				█	█	█	█	█	█	█	█	█
Collection of pre-, mid-, post-, and follow-up data				█	█	█	█	█	█	█	█	█
Data analyses										█	█	█
Dissemination (conference presentations & publications)												█

*Estimated participant recruitment flow, in even numbers for randomization

1.M.a. Summary: Significance and Innovation

- Treatments that bridge adolescence through early adulthood are needed to prevent the developmental plateau, and often regression, attributed to the service ‘cliff’ and lack of effective treatments during this developmental period for those without co-occurring intellectual disability. EASE was specifically developed for this population and developmental period, using a participatory action approach to ensure it meets the needs of teens and young adults with ASD (and their parents), and to maximize feasibility and ultimate dissemination.
- Consistent with the current emphasis in treatment development research adopted by the National Institutes of Health, EASE emphasizes engaging an underlying target mechanism, namely ER. By improving emotion awareness and mindfulness, EASE is hypothesized to improve ER directly, which we believe will have downstream effects of a host of behavioral problems including aggression, hostility, and depression, as well as functional independence.
- The modularity and flexibility of EASE permits therapists to make the program highly personalized, which is critical given the tremendous clinical heterogeneity in this population.
- The study design is rigorous, with use of an active control condition, blind raters, and two sites. Inclusion of the active control is much stronger test than the traditional waiting list control. By having two sites, we are able to reach the target sample size and also ensure that EASE can be implemented with fidelity across sites and providers, which is critical for subsequent dissemination. Further, by ensuring equivalence across the sites in all aspects of study implementation (e.g., recruitment, data collection) we will be well-prepared for subsequent evaluation of mediation in a fully powered multi-site trial.