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Occupations as an Outcome Measure in a Clinical Trial: Fragile X Syndrome and Sertraline

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This project, written under the direction of the candidates’ faculty advisor and approved by the chair of the Master’s program, has been presented to and accepted by the Faculty of the Occupational Therapy department in partial fulfillment of the requirements for the degree of Master of Science in Occupational Therapy. The content, project, and research methodologies presented in this work represent the work of the candidates alone.

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Abstract

Fragile X Syndrome (FXS) is the most common form of inherited intellectual and developmental disability, and a known genetic cause of autism. Individuals with FXS present with deficits in cognition, social skills, behavior, language and sensory processing skills; all of which are commonly assessed through standardized and norm-referenced assessments. However, these outcome measures are sometimes not sensitive to contextually based changes in daily life. Further, there is limited research employing qualitative methods in the FXS literature. The purpose of this research was to examine family perspectives collected via semi-structured interviews as part of a randomized controlled medication trial of sertraline (Zoloft) on children two to six years old diagnosed with FXS. The constant comparison method was used to analyze differences in family expressions of their child’s improvements over the course of the 6-month clinical trial. Twelve interviews were analyzed, six-treatment, six-placebo, and all coding was done blind to group assignment. Results indicated greater improvements in the treatment group when compared to the placebo group in: anxiety, receptive / expressive communication, maladaptive behaviors and some sensory issues. These preliminary findings warrant a need for further research with a larger sample.
Fragile X Syndrome (FXS) is the most common form of inherited intellectual and developmental disability (IDD) and is also the most common genetic form of autism spectrum disorder (ASD) (Hagerman et al., 2010; National Fragile X Foundation [NFXF], 2015). Shared characteristics of ASD and FXS include limited social interaction, language deficits and communication impairments, sensory processing differences, anxiety, and maladaptive behaviors (Case-Smith & Arbesman, 2008). Living with FXS not only affects the individuals diagnosed with FXS, but also their families. Raising a child with FXS can significantly impact the families’ health and quality of life, their ability to navigate health and educational systems, ability to overcome social stigma, define the family identity, and establish family occupational roles (Tomlin & Swinth, 2015). While families are learning about FXS through their own disability experience, there is little representation of family voice and context via qualitative methods in the research literature. While standardized and norm-referenced assessments and parent checklist are widely used as outcome measures and provide quantitative data, their application in a clinical trial of sertraline with young children with FXS may not be appropriate to measure contextual changes. These outcome measures are limited in context and not reflective of functional changes for the IDD population. To date, research literature focuses primarily on quantitative methods and the medical model. Furthermore, the use of standardized and norm-referenced outcome measures leaves populations with IDD vulnerable to flooring effects. By including families’ experiences of FXS, future treatments can be geared toward improving the child with FXS’s participation in desired occupations.
The purpose of this research is to examine family perspectives collected during baseline and follow-up interviews as part of a randomized, double-blinded, six-month, controlled medication trial of sertraline (Zoloft) on children two to six years old diagnosed with FXS. Semi-structured interviews were used to understand family expressions and contexts of their child’s improvements over the course of the clinical trial. This qualitative data may prove to be a more sensitive measure in contrast to standardized measurements, which show limited, change over time with IDD populations.

**Literature Review**

The following literature review examined research conducted in various areas involving FXS. Topics included detailed information about FXS, treatments for FXS including behavioral and pharmacological interventions, how FXS affects families, and outcome measures used to help better understand FXS. Additionally, the literature review discussed the completed, randomized controlled trial research study in which the interviews were conducted. This proposal highlighted the importance for further research to be done on FXS and family perspectives.

**FMRP and Physiology**

FXS is caused by an expanded CGG repeat which leads to cellular dysregulation of the Fragile X Mental Retardation Protein (FMRP) (Hagerman, Hoem, & Hagerman, 2010). The lack of the FMRP in FXS causes dysregulation and often the overexpression of its target genes. Mutations in the *FMRI* gene lead to transcriptional silencing and loss of FMRP expression resulting in FXS. Farzin et al. (2006) explained that FMRP is important for the development and maturation of dendritic spines and synaptic connections. In other words, the lack of FMRP is
responsible for the cognitive, physical, and behavioral impairments seen in patients with FXS, making it the most common heritable form of mental retardation.

**Heritability and Prevalence**

In the general population, approximately one in 3600 males and one in 6000 females have FXS (Farzin et al., 2006). FXS has a premutation and a full mutation. In premutation, the CGG-repeat ranges from 55 to 200 repeats in a specific region of the *FMR1* gene. In the full mutation, this same region of the *FMR1* gene spans the length of greater than 200 repeats (Hagerman et al., 2010). The more CGG repeats found in the genetic code, the less FMRP is expressed which causes relatively more cognitive, physical, and behavioral deficits. When a premutation female carrier has a child there is an increased chance that CGG-repeat will expand into a full mutation. Most individuals with a premutation are neither developmentally disabled nor do they have autism. However, a subgroup of individuals with the FXS premutation do experience cognitive, emotional and/or behavioral involvement, but with less severity than those possessing full mutation of FXS.

Wang et al. (2010) assert there is strong association between FXS and autism when examining the molecular and symptomatic overlap between the two disorders. Nearly 40% of individuals with FXS also have ASD and 10% of individuals with ASD also present with FXS (National Fragile X Foundation, 2015). The overlap in neurotransmission and symptomatology affords popular treatments for the broader spectrum of autism to possibly be used in treating those with FXS (Hagerman, Lauterborn, Au, & Berry-Kravis, 2012).
FXS with and without Autism

FXS can occur with or without autism. In particular, FXS is the most common single gene cause of autism, responsible for 2% to 6% of all cases of autism. For individuals diagnosed with FXS, Wang, Berry-Kravis, and Hagerman (2010) reported the prevalence of ASD to be approximately 18%–36%. The National Fragile X Foundation (NFXF) with the Center for Disease Control report that as of 2016, the prevalence of FXS with ASD is 46%, demonstrating an increase in this comorbidity (NFXF, 2016) when compared to the prevalence in Wang, Berry-Kravis, and Hagerman’s research (2010). In comorbid ASD and FXS, Wang et al. (2010) emphasized that such individuals present higher degrees of severity of symptoms and deficits in overall functioning when compared to children diagnosed with FXS alone.

Males vs. Females with FXS

Males and females inherit the premutation and full mutation of the FMR1 gene differently (Hagerman et al., 2010). A female with a premutation could have inherited a FXS premutation from either parent. In male, the premutation derives from the biological female carrier. However, all children having full mutation, regardless of gender, have a biological carrier mother. Also, the propensity for transmission of a full mutation allele increases with an increasing CGG repeat number in the mother. Decreased levels of FMRP correlate with increased clinical implications including physical, cognitive and structural/functional brain involvement. Children with FXS who do not meet the criteria for an ASD diagnosis still nonetheless often exhibit one or more autistic features such as hand flapping, poor eye contact and tactile defensiveness.
One study by Farzin et al. (2006) noted some key differences between males and females with FXS. For both genders, premutation carriers are at higher risk for developmental problems, particularly those who present clinically with behavioral difficulties. FXS is less likely to occur in females and its presentation is usually less severe. Also, most female carriers of FXS are less likely to experience developmental or behavioral problems in childhood. In contrast, males with full mutation FXS show greater instances of maladaptive behaviors and developmental deficits (Wang et al., 2010). Males have a higher rate of comorbid FXS and ASD. The NFXF reports in 2016 that 46% comorbidity occurs in males versus 16% in females (NFXF, 2016). In an older 2010 study, the percentage of both FXS and ASD was 5% in females while it occurred as 10-15% of the time in male carriers (Wang et al., 2010), showing a dramatic increase of heritability in both males and females in the last few years.

For those with both FXS and autism, there is a spectrum of involvement both cognitively and behaviorally, with intelligence quotient (IQ) values ranging from severely intellectually impaired to typical, particularly in females. However, there is a strong association between low IQ and the autism diagnosis in both males and females with FXS (Hagerman et al., 2010).

**Phenotype of FXS**

**Behavioral.** Behavioral issues are a key feature of the FXS phenotype, encompassing attention difficulties, hyperactivity/impulsivity, social anxiety, repetitive/perseverative behaviors, poor eye contact, self-injurious behavior (SIB), aggression, irritability, and sleep problems (Kronk et al., 2010; Kurtz, Chin, Robinson, O’Connor, & Hagopian, 2015; Wang et al., 2012). Anxiety-related symptoms common in individuals with FXS include shyness, social phobia, obsessive compulsive disorder (OCD)-like symptoms, hyperarousal, and attention-deficit
hyperactivity disorder (ADHD)-like symptoms (Berry-Kravis et al., 2013). Common forms of SIB in individuals with FXS include finger/hand biting, head/self-hitting, picking/pulling skin/hair, and self-scratching (Kurtz, 2015). Recent prevalence estimates for SIB in males with FXS range from 39% to 79% (Kurtz, 2015). Parents of children with FXS report that SIB and aggression are among the most stressful and life impacting behavioral challenges as they often result in injury to self or others (Berry-Kravis et al., 2015).

Physical. The typical physical features of FXS in both males and females are long, narrow face, prominent ears, highly arched palate, hypotonia, hypermobility in the metacarpophalangeal joints, scoliosis, and flat feet (NFXF, 2016). Macro-orchidism, abnormally large testes in males and enlarged ovaries in females, are a common phenotype observed in individuals with FXS but is rare before puberty and becomes more evident as the child grows (NFXF, 2016). Ocular problems present in children with FXS include strabismus, or “lazy eye”, and ptosis, or drooping eyelids, both of which are thought to be caused by low muscle tone. Additionally children with FXS may have nystagmus, shaking of the iris in a back and forth motion, which may in turn cause near- or far-sightedness (NFXF, 2016). Cardiac abnormalities which include “functional” or “innocent” murmur can lead to mitral valve prolapse in individuals with FXS (NFXF, 2016).

Cognitive. Individuals with FXS exhibit a range of cognitive problems such as intellectual disability and deficits in social cognition and executive functioning (Berry-Kravis et al., 2015). Intellectual disabilities are characterized by significant limitations in both intellectual functioning and in adaptive behavior including social cognition. Intellectual functioning and adaptive behavior are needed for many everyday social and practical skills and interactions. FXS
is the most common inherited cause of intellectual delays with an average IQ of 40 (Klusek et al., 2015; Merenstein et al., 1996). Males with FXS display mild to moderate intellectual delays and demonstrate adaptive skills in the low-average range (Klusek et al., 2015). Approximately 50% of women with full mutation FXS have IQs in the borderline or mild intellectual disability range (Hagerman, Jackson, & Amiri, 1992).

Social cognition refers to the processing of information about the social world, e.g., the ability to recognize differences in people’s knowledge or perspectives (Farzin, Rivera, & Hessl, 2009). Impairments in some aspects of social cognition exceed the impairments seen in other domains, especially in individuals with comorbid FXS and ASD (Farzin et al., 2009). Executive function involves the management of cognitive processes such as working and explicit memory, sequential processing, reasoning, task flexibility, problem-solving, planning, and execution. There is compelling evidence that executive function deficits are highly characteristic of individuals with FXS (Berry-Kravis et al., 2013).

**Language.** Language impairments common in individuals with FXS are seen in the following areas: prelinguistic, receptive, expressive, and speech intelligibility (Berry-Kravis et al., 2013; Finestack, Richmond, & Abbeduto, 2010). Children with FXS that present with language impairments also show high rates of verbal perseveration and bursts of rapid, poorly articulated speech (Berry-Kravis et al., 2015). Expressive language deficits common in individuals with FXS often inhibit the types of social interactions that foster language growth and development in typically developing children. Lower IQ and more severe ASD symptoms are associated with more serious language problems (Berry-Kravis et al., 2013).
Sensory. Sensory processing deficits common in children with FXS also influence occupational performance, including self-care, school functioning, and play. Deficits in sensory processing manifests as unusual responses to typically neutral input such as noise, tactile, visual and olfactory stimuli (Hagerman, 1996). Clinical observations of behavioral symptoms of FXS such as social phobia, anxiety, hyperarousal and hyperactivity have been thought to reflect difficulties in sensory processing, the process in which the nervous system receives input from the senses and translates them into appropriate motor and behavioral responses (Baranek, Chin, Hess, Yankee, Hatton, & Hooper, 2002). Sensory processing is critical for understanding the environment and sense of self, including sight, hearing, taste, touch, smell, body awareness and balance (Baranek et al., 2002). Miller et al. (1999) found that children with FXS manifested the most severe sensory processing disorders of all the clinical groups in their studies including ASD and ADHD.

The Importance of Family Perspective on FXS

Brett (2002, p. 827) emphasized that “parents often hold the key in accessing their child’s experiences and providing essential insight into their child’s world.” The lives of children with FXS and parents closely influence one another. Therefore, parents’ concerns are informative and essential to developing an alternative model for examining the challenges of raising children with disabilities, including children with FXS. Detailed parent perspectives can illuminate a child’s behavior in the home and social issues that they may face. Brett (2002) explains that society must dismantle the stigma of disability and promote a socially aware, active and inclusive culture.
Research suggested that problem behaviors of children with FXS have the greatest impact on parents and families as compared to those with cognitive impairment (Bailey Jr. et al., 2000). Because biological mothers of children with FXS are carriers of the premutation of FXS, these women are more genetically susceptible to depression, social anxiety, and possibly unstable affection toward the child (Abbeduto et al., 2004; Bailey et al., 2008). Fathers of children with FXS are also affected by child-related stress, although mothers are usually considered as playing a more important role in parenting (Hartley, Seltzer, Head, & Abbeduto, 2015). Although research has shown the predisposed risk in parents’ mental health in families with FXS, other research suggested differing findings by examining family perspectives. One study examined the perceived quality of life in mothers of children with FXS through self-report. The findings indicated that mothers of children with FXS did not have a perceived lower quality of life than average women. Researchers proposed although it was reported that parents faced challenges and stressors in an unsupportive social environment, mothers of children with FXS held hope in the disability, which might result in positive perspective of quality of life (Wheeler, Skinner, & Bailey, 2008). Furthermore, Hauser, Kover, and Abbeduto (2014) conducted a short-term longitudinal study to examine the bidirectional relationships between maternal mental health status, maternal stress, family environment, and behavioral functioning of children with FXS. The study suggested that maternal mental health status had no significant relationship with changes in levels of the child’s challenging behavior. Contrary to popular belief, high rates of the child’s challenging behavior was found to be associated with improvements in maternal depression over time. In turn, heightened levels of challenging behaviors increased maternal closeness toward the child over time (Hauser, Kover, & Abbeduto, 2014). Researchers explained
that heightened challenging behaviors gather additional external support, either from the father, other family members, or even professionals. These additional supports relieve emotional burdens of the mothers; therefore potentially decrease symptoms of mental illness. Moreover, the positive relationship of closeness and challenging behavior can be explained by the increased time spent and sense of protection from the mothers with their children (Hauser, Kover, & Abbeduto, 2014). These unanticipated results represent a need to further examine family perspectives in order to provide a contextual base to the study.

**Treatment of FXS**

**Behavioral intervention.** A variety of professionals participate in behavioral interventions for children with FXS. Practitioners often include special education teachers, occupational therapists, speech and language therapists, physical therapists, and behavioral therapists. An interdisciplinary approach may be adopted in the intervention process and is typically outlined in an Individualized Educational Plan (IEP) in a school-based setting.

Despite extensive research on the behavioral phenotype of FXS, relatively few studies have been conducted on the effectiveness of behavioral treatments for children with FXS (Hagerman, 2009). Researchers believe the lack of research in this domain is due to overemphasis of biological factors of FXS (Moskowitz, Carr, & Brook, 2011). Parents of children with FXS assume that their children’s problem behavior is permanently determined by the underlying FMRP deficiency. This leads to the belief that medical treatment is a more superior approach than behavioral treatment (Hall, 2009). Behavioral interventions for FXS are generally individualized and they normally utilize their own clinical experience in association with their knowledge in typical behavioral phenotype of FXS to guide their treatment approaches.
OCCUPATIONS AS OUTCOME MEASURE IN A CLINICAL TRIAL

(Hagerman, 2009). Contemporary strategies that treat ASD and other developmental disabilities have shown positive outcomes on the behaviors of children with FXS who present behaviors similar to children with ASD such as hyperarousal, impulsivity, and SIB (Hagerman, 2009).

Intervention methods that aim to improve behaviors of children with FXS include applied behavior analysis (ABA) and environmental modifications. Behavioral-specific models, such as ABA, are used in ASD and FXS treatments. This includes the functional behavioral analysis and the antecedent-behavior-consequence models. These are utilized to address and replace maladaptive behaviors through positive reinforcement of adaptive behaviors (Hills-Epstein, Riley, & Sobesky, 2002). Studies also show that modified home environments are associated with better adaptive behavior and fewer autistic behaviors for children with FXS (Glaser et al., 2003; Hessl et al., 2001). These studies suggest that modifications in home and classroom environments tailored for children with FXS may lead to better behavioral outcomes.

Treatments comparable in treating ASD are applicable to children with FXS as well. Available models include: the Treatment and Education of Autistic and Related Communication-Handicapped Children (TEACCH) model, the Denver model, and Pivotal Response Training (PRT). Although these are well-established models for ASD, Hagerman (2012) states that these treatment models have also been helpful for many children with FXS. Social issues for children can be addressed by behavior modification interventions aimed at improving social eye contact. As social problems can also be caused by heightened responses to sensory stimuli, addressing the sensory input by reducing environmental stimuli and improving sensory coping skills has the potential to generate improvements in behavior. (Hagerman, 2009).
Although behavioral intervention strategies for FXS typically are based on ASD treatment, the potential of developing effective behavioral intervention specified for FXS has been supported by a number of studies. For instance, Moskowitz et al. (2011) collaborated with three families with children with FXS and developed a set of individualized behavioral treatments strategies. Some examples of interventions included manipulating setting events, increasing predictability, providing choices, social stories, etc. Of the three children who participated in the study, all three showed substantial behavioral improvements in the most problematic behaviors identified by the mothers. This research indicates that although FXS is known as a genetic condition that is presumably unalterable, the potential of improving problem behaviors should not be overlooked. Additionally, Kurtz, Chin, Robinson, O’Connor, and Hagopian (2015) conducted a consecutive case-series analysis that reports on functional analysis and treatment of problem behavior of nine children with FXS. All analyses were done using multi-element designs that included attention, demand, and play conditions. The findings suggest that functional-based behavioral interventions that are effective for individuals with IDD are also effective for children with FXS.

Evidence supports combination treatment models that include behavioral intervention and pharmacological treatments (Reiss & Hall, 2007). Therefore, in addition to occupation-based behavioral therapy, some parents choose to have their child with FXS take medications, including selective-serotonin uptake inhibitor, or SSRIs.

**Medical intervention - Selective-serotonin uptake inhibitors (SSRIs).** SSRIs work by blocking the reabsorption of serotonin, thus leaving more serotonin available to improve mood (Brown & Stoffel, 2011). It is hypothesized that children with FXS have serotonin dysregulation
similar to children with ASD (Chugani, 1999; Hanson, 2014). The findings in the Hanson (2014) study suggest that use of SSRIs may be helpful in serotonin regulation for children with FXS. In particular, sertraline (trade name Zoloft), is “considered one of the most potent inhibitors of serotonin reuptake. Additionally, sertraline significantly prevents dopamine reuptake” (Hanson, 2014, p. 113). Because sertraline is one of the most potent among SSRIs, it is possible that it is also the most effective SSRI treatment for children with FXS.

**Current use in FXS.** SSRIs are currently being prescribed to treat some children with FXS. According to Hagerman et al. (2009), SSRIs given at typical doses were helpful more than half the time in treating anxiety and other problems related to anxiety in children with FXS. SSRIs were shown to be helpful on the basis of survey reports and clinical trials (Hagerman et al., 2009). SSRIs can be helpful in changing behaviors and language development seen in children with FXS. Winarni et al. (2012) used retrospective chart review of 45 children with FXS between the ages of 12-50 months to measure the effects of sertraline. The children in the study experienced anxiety, irritability, and problems with social interaction. The 11 children who received sertraline had their medical charts compared with the 34 children who did not receive sertraline. The children who had received sertraline were found to have decreases in anxiety, irritability, and problems with social interaction. All children in the study were found to have improvements in language development; however, the children in the sertraline group displayed significant improvements in language development over the non-sertraline group. Finally, according to Hess et al. (2016), SSRIs are helpful in treating the phenotypical manifestations of FXS including communication and intellectual deficits, anxiety, and sensory processing challenges. While SSRIs are helpful in treating these deficits seen in FXS, no previous studies
have been done on children with FXS younger than five years old. Thus, the results from Hess et al.’s (2016) study show promise for sertraline use in children with FXS under the age of five, particularly in the areas of social participation and overall development. The findings in the aforementioned studies are significant as quantitative data supports the use of sertraline in children with FXS for language development, decreasing maladaptive behaviors, and social participation. However, the outcome measures used in those studies lack a qualitative component sensitive enough to detect changes in daily life and overall functioning for IDD populations.

**Outcome Measures Commonly Used to Assess FXS and ASD**

To date, clinical trials on subjects with FXS have focused the evaluation of their outcomes with a battery of standardized assessments and structured parental surveys rather than qualitative data. Some frequently employed outcome measures include: Sensory Processing Measure (SPM) and Sensory Processing Measure-Preschool (SPM-P), Mullen Scales of Early Learning (MSEL), the Standardized Language Sampling Procedures (SLSP), The Aberrant Behaviors Checklist (ABC), and the Social Responsiveness Scale (SRS) (Berry-Kravis et al., 2013, Hessl et al., 2016). Although these standardized assessments are widely used and offer sound psychometric and quantitative data, they lack sensitivity to clinically meaningful change, lack context and family voice, and may not be applicable for lower-functioning individuals (Berry-Kravis et al., 2013). Moreover, Berry-Kravis et al. (2013) note that outcome measures that have been developed for symptom-based clinical trials in behaviorally defined disorders, such as autism and ADHD, might not be sufficiently sensitive or specific for disease-oriented interventions in
FXS. The gap between quantitative outcome measures and the daily lived experience of parents of children with FXS creates a need to incorporate interviews in the research procedure.

Incorporating semi-structured caregiver interviews into the research procedure could provide context and voice for changes, are occupation-centered, explain the daily life impact of disability, and may identify potential outcomes for intervention in clinical trials. Hess et al.’s 2016 “Family Meanings” study argues that inclusion of a sociocultural perspective within the context of a clinical trial affords consideration of a dynamic view of development - that is, simultaneous consideration of biological and sociocultural factors with the application of a bioecological framework. Therefore, the use of interviews is suggested to capture family voice and life with FXS in context. The use of parent interviews as a tool to measure outcomes in clinical studies may enhance practitioners’ and clinical researchers’ understanding of the complexities families may face. Parent interviews can also inform the scope and focus of outcome measures by identifying the most meaningful outcome variables to monitor and establish as behavioral and pharmacological treatment goals (Tomlin & Swinth, 2015).

**UC Davis MIND Institute Randomized Clinical Trial**

A randomized controlled trial of sertraline was completed at the UC Davis, Medical Investigation of Neurodevelopmental Disorders (MIND) Institute (Hess et al., 2016). The results of Hess et al.’s 2016 study showed that no significant differences were observed in the MSEL expressive language subscales and CGI-I primary outcome measures for sertraline compared to placebo. Secondary measures revealed significant improvement in social participation on the SPM-P. Fine motor and visual perception were also significantly improved on the MSEL age equivalent scores for the sertraline treatment group when compared to the placebo group. Post
hoc analysis combining all MSEL age-equivalent scores (expressive, visual, receptive and fine motor) showed overall significant improvement. Results suggest sertraline had significant positive effect on social improvements and overall development. Adverse events (AEs) were similar between sertraline and placebo groups with no significant differences in characteristics of AEs observed between the groups.

Families enrolled in the UC Davis MIND Institute sertraline clinical trial participated in semi-structured interviews at baseline and post testing. The baseline interviews posed questions focused on living with FXS and the impact on daily family life. Upon conclusion of the clinical trial, while the families were still blind to whether they were randomized to either the sertraline treatment or placebo groups, a second set of interviews were conducted asking families to reflect upon areas of possible improvement for their child who participated in the study (e.g. activity level, anxiety, sensory processing and communication) and whether there had been any subsequent impact on family life.

After the six-month trial, children in the sertraline group were reported to have a significant increase in their social participation as compared to the placebo group. Social participation items on the SPM-P included: family outings, gatherings, activities with friends, and family errands (Hess et al., 2016). In addition to the SPM-P, conversational interviews at baseline and post intervention explored the complexities of daily life, experiences, and family meanings associated with various phenotypic manifestations of FXS (e.g. language / communication, behavior, sensory processing, and anxiety) (Hess, Ching & Hagerman, 2014). Via semi-structured interviews, families were asked to share their stories and experiences in their own words as a first-person account that focused on family hopes and meanings for participation
in this clinical trial rather than responding to a set of predetermined response choices. The interview results highlight the importance of how their child’s social participation greatly affects the understanding of family perspectives in the treatment of FXS. This research study aimed to find the potential for interviews to provide a deeper understanding of the lived experience of families.

**Conclusion**

FXS is the most common form of inherited intellectual disability. Typical manifestations of FXS include sensory, language, behavioral, and social deficits. These deficits affect the family dynamics, and increase family stress and desire to seek effective interventions. However, medical management research for young children with FXS is emerging. Qualitative research examining family perspectives on the impact of medication on everyday functioning in young children with FXS is not currently part of the treatment literature. This research utilized semi-structured interviews to empirically examine parental perspectives regarding medication effectiveness in everyday life contexts. While there has been a vast amount of quantitative research conducted on FXS, there is limited qualitative research. In addition, quantitative assessments lack sensitivity to clinically meaningful change and context. Rather, family perspectives, as a qualitative outcome measure have the potential to enrich analysis of clinical trials as an additional supplement to the current outcome measurement battery. The gaps in the research and the findings of previous sertraline studies support the need for further research surrounding FXS and family perspectives of raising a child with FXS.
Statement of Purpose

Statement of Problem

As research into potential treatment methods for FXS grows, the lack of parental voice in the understanding of this genetic disorder’s treatment, intervention, and proposed outcome measures persists, resulting in a gap in current knowledge. The gap highlights the need to utilize parental perspectives through interviews as a tool to contribute to and expand upon current standardized outcome measures. Outcomes measures used currently to assess FXS are limited in scope and context, and lack the voices of families of children with FXS. Moreover, current standardized measures lack sensitivity to reflect changes over time and improvements in the context of daily living.

Significance and Purpose of Study

The research aimed to provide a new lens into the perspectives of families and their experiences. Semi-structured, open-ended questions were used during the interviews with families participating in the clinical trial. The interview data was used to gauge whether there were experiential differences in activity level, communication, behavior, and sensory processing between the sertraline treatment group and placebo group. To a larger degree, the results of this study may demonstrate the significance of qualitative information from interviews to support clinical trials and will contribute to the growing need for re-evaluation of outcome measures used in future clinical studies. The purpose of this study was to examine family perspectives and how interviews can be used to understand family expressions and contexts of their child’s reported improvements over the course of the clinical trial. This qualitative data may be a more sensitive
measure in contrast to standardized measurements, which capture limited change over time within IDD populations.

**Research Question**

The research question that guided this study was: Can qualitative interview methods serve as an outcome measure capturing changes in occupational performance between treatment and placebo groups?

**Theoretical Framework**

The theoretical frameworks that guided this study were Vygotsky’s sociocultural theory and the Person-Environment-Occupation (PEO) model (Law et al., 1996). These frameworks are related to this research study as they addressed the social, cultural, and environmental factors that both children with FXS and their families encountered on a daily basis (Hessl et al., 2001). Children with FXS have a genetic condition that manifests in a phenotypic expression of intellectual and functional disabilities (Wang, Berry-Kravis, & Hagerman, 2010). However, biology is not the sole determining factor of one’s functioning, therefore it is vital to also consider social and cultural factors in the growth and development of children with FXS.

Vygotsky’s sociocultural theory suggests that children’s cognition improves through social and cultural interaction (McLeod, 2016). This theory relates to the research as it incorporates family perspectives as a way to better understand FXS and potential treatment options. Each family’s social and cultural background influences the child’s development and experience of the world. According to McLeod (2016), “individual development cannot be understood without reference to the social and cultural context within which it is embedded.” The sociocultural theory guided this research study by showing how differing social and cultural
views affect both children with FXS and their families, and how those views can be useful in helping to understand FXS in a larger population.

Additionally, Vygotsky (1978) emphasized that learning and development are dynamic systems that go hand-in-hand. While the child is developing biologically, they are also learning from external sources like social interaction and their cultural environment. This theory relates to families of children with FXS as certain social and cultural interactions, such as occupational therapy, behavioral therapy, and special education, are likely impactful factors in the child with FXS’s learning and development. While these children will certainly have biological development and learning associated with FXS as a genetic diagnosis, it is critical to include the sociocultural theory as it brings an external component into the picture.

Just as the sociocultural framework creates an important grounding for the research in the dynamic interactions of biology and the environment, the PEO model also influences this study. The PEO model aims at optimizing the interaction and identifying the best fit between the person, environment, and occupation. This model guides occupational therapy intervention by providing a specific understanding for how the environment can have an effect on the person, and how they participate in their desired occupations. The PEO model also relates to families of children with FXS, as some environmental factors can have a great effect on how both the child with FXS and their families are able to participate in daily life. According to Law et al. (1996), the person develops dynamically and is always interacting with their environment. Through this model, occupational therapy intervention is targeted towards finding the best fit for the person in a specific environment. This relates to families of children with FXS, as it is important to understand that the physical, social, and cultural environment can all have a positive or negative
effect on how children with FXS and their families participate in daily occupations. By identifying ways to adjust the environment for children with FXS and their families, their ability to participate in their desired occupations will be further enhanced.

Methodology

Design

This was a qualitative research study that employed interview methods. Semi-structured interviews were conducted at baseline and again at post-testing as part of the UC Davis MIND Institute randomized controlled trial of sertraline study, and audio-recorded (Hess et al., 2016). This research utilized data from 12 post-interviews (6 placebo and 6 treatment) conducted upon completion of the 6-month randomized controlled trial (see Figure 1). At the time of the post-interviews, families were still blind to their group assignment in the randomized controlled trial. Additionally, for this analysis, researchers were blind to the group assignment (6 placebo and 6 treatment). The researchers then transcribed interview recordings verbatim using ExpressScribe.
OCCUPATIONS AS OUTCOME MEASURE IN A CLINICAL TRIAL

Figure 1. Flow chart of UC Davis MIND Institute sertraline and FXS randomized clinical trial. Researchers conducted baseline interviews and assessments and then randomly grouped participants into either the treatment or placebo group. After the 6-month clinical trial, a post interview and assessment was conducted. This research focused on the post-interviews.

Population

The target population for this study was the parents or caregivers of children ages two to six years with FXS enrolled in the UC Davis MIND Institute’s randomized clinical trial of sertraline (Hess et al., 2016). A snowball recruiting procedure was used to gather the participants for the completed clinical trial at the UC Davis MIND Institute.

Ethical Considerations

Due to the sensitive nature of the interview data, private information was protected by assigning anonymous identification numbers to each participant and omitting names of children
and parents during the transcription process. Interview data was stored in a secure, locked location that was only accessible to researchers on site. The research team and assistants signed confidentiality statements (see Appendix A for interview protocol). Once data was anonymized, it was imported into Dedoose (www.dedoose.com), a secure, web-based mixed methods software application, for analysis. To further protect participants, data was made accessible to research members only via password protection.

Data Collection

The interviews were completed either at the UC Davis MIND Institute or via phone with an occupational therapist. Interviews were 45-60 minutes in length and were conducted in a conversation format and audio recorded on an iPad. The interview data base was obtained via written permission from the principal investigator of the UC Davis MIND Institute FXS and sertraline study. The Dominican University research team and assistants transcribed interviews verbatim using ExpressScribe transcription software. Transcriptions were then uploaded and stored in Dedoose. The Dominican University principal investigator assigned 12 out of 30 post clinical trial audio files to the researchers to code and analyze (6 placebo group and 6 sertraline group, all male subjects). Researchers were blind to group assignments of 12 audio files until the final stage of the data analysis process.

Data Analysis

The goal of the data analysis was to discover groupings, themes, or patterns from interview information including improvements in daily life and occupations. The constant comparison method (Corbin & Strauss, 1994) drove the data analysis, and the research team developed codes based on emergent themes via consensus and inductive analysis. Through
inductive analysis, themes, patterns, and categories “emerged out of the data rather than being imposed on them prior to data collection and analysis” (Dye, Schatz, Rosenberg, & Coleman, 2000, p. 4). Analysis and interpretation of the data were guided by the chosen theoretical frameworks to provide an in-depth, sociocultural and occupation-centered context.

Researchers began the initial categorizing and labeling of transcript excerpts. Observations from the interviews were compared and bits of data were grouped based upon similarities (Dye, Schatz, Rosenberg, & Coleman, 2000). Through this, researchers assigned meaning to the data by linking the interviewee’s responses to recurring concepts and categories. Categories were reviewed and refined following the initial category generation. This refining process clarified the initial categories, which were broad in scope to begin with, but became more precise through the process (Dye, Schatz, Rosenberg, & Coleman, 2000). Researchers then created codes and operationalized definitions for these categories (see Table 1). These definitions ensured codes were consistently applied. Each researcher independently coded three transcripts and used content analysis to compare primary patterns in the data and incidents. Then the researchers independently reviewed all coded transcription excerpts across all 19 thematically-based codes. Themes were operationalized with further clarified code definitions (as necessary) and re-categorized according to patterns discovered in the data. Through consensus coding, 100% agreement was reached by all four researchers across the 345 coded excerpts during analysis.
### Operational definitions of Codes

<table>
<thead>
<tr>
<th>Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety Improved</td>
<td>Decreased anxiety features, decreased recovery time after experiencing anxiety, shyness, social phobia, obsessive compulsive disorder (OCD)-like symptoms, hyperarousal, and attention-deficit hyperactivity disorder (ADHD)-like symptoms</td>
</tr>
<tr>
<td>Anxiety Not Improved</td>
<td>No change or worsening in anxiety</td>
</tr>
<tr>
<td>Anxiety Proactive Strategies</td>
<td>Proactive strategies used by families that help manage anxiety</td>
</tr>
<tr>
<td>Behavior Improved - Less</td>
<td>Decrease <em>Less</em> fussing, crying, upset, frustration, screamings, tantrums, finger/hand biting, head / self hitting, picking/pulling skin/hair, and self-scratching</td>
</tr>
<tr>
<td>Behavior Improved - More</td>
<td>More: attention, independence, purpose</td>
</tr>
<tr>
<td>Behavior Not Improved</td>
<td>No improvement; worsen in behavior; Increase in meltdowns, hyperactivity, rigidity</td>
</tr>
<tr>
<td>Behavior Proactive Strategies</td>
<td>Use of schedules, tokens, reinforces</td>
</tr>
<tr>
<td>Communication Improved Expressive</td>
<td>Verbal, sign, gestures, getting wants &amp; needs met, hand leading</td>
</tr>
<tr>
<td>Communication Improved Receptive</td>
<td>Understanding verbal or gestural info, understanding directions, following 1-step commands</td>
</tr>
<tr>
<td>Communication Not Improved</td>
<td>No improvement; worsen in communication; Decreased meaningful communication</td>
</tr>
<tr>
<td>Communication Proactive Strategies</td>
<td>Picture Exchange Communication System (PECS), device, schedule, reinforces</td>
</tr>
<tr>
<td>Community / Social Improved</td>
<td>Increased ability in participation in the community such as grocery shopping, visiting the parks; improved behavior at parties, family and social events</td>
</tr>
<tr>
<td>Community Social Not Improved</td>
<td>Problem in going out in the community, parks, parties, family gatherings, and social events</td>
</tr>
<tr>
<td>Functional Improvement</td>
<td>Increased ability in performing ADLs; increased safety awareness</td>
</tr>
<tr>
<td>Functional Not Improved</td>
<td>Decreased performance in ADLs; decreased safety awareness</td>
</tr>
<tr>
<td>Sensory Improved - Less</td>
<td><em>Less</em> self-stimulation, less seeking, less defensiveness, less avoiding, hyperarousal, hyperactivity, sensitivity to typically neutral sensory stimuli such as noise, tactile, visual and olfactory stimuli (Hagerman, 1996).</td>
</tr>
<tr>
<td>Sensory Improve - More</td>
<td>More tolerant, more exploratory of sensory etc.</td>
</tr>
<tr>
<td>Sensory Not Improved</td>
<td>Lack of improvement/worsen in sensory</td>
</tr>
<tr>
<td>Sensory Proactive Strategies</td>
<td>Sensory diet activities &amp; techniques (motor breaks, sensory routines)</td>
</tr>
</tbody>
</table>
Results

The interviews were analyzed to determine whether or not there were differences in the aforementioned codes between the sertraline treatment and placebo groups. Percentage of codes that were applied to the sertraline treatment group and placebo group are represented in Figure 2. Codes are represented in italics and exemplar quotes are noted as stated by the families. Any names noted are pseudonyms.

Anxiety

Our data showed that the application of code *Anxiety Not Improved* were found more often (79%) in the placebo group than the sertraline treatment group (21%). Application of *Anxiety Improved* was more even, with 5/9 (56%) applied in the sertraline treatment group and 4/9 (44%) in the placebo group. Parents’ descriptions of their child’s improvements in anxiety included an increase in coping with things or situations that caused anxiety. For example, a parent shared, “…because he knows oh I can climb this, I’ve done that.” Meanwhile, other parents noted that their child’s anxiety did not show improvement. A parent of one child remarked:

He grabs you into a death hug. And it took a while to finally get him away from you a little bit so he can actually feel the water. That seems like a change for me. Like he’s more clinging in the water.

Proactive coping strategies for anxiety were noted among the children. Another parent shared, “it stressed him out, taking his blanket and sucking on it. [It is] the only thing to calm him down.”
Behavior

Approximately 90% of Behavior Improved (Less) were coded in the sertraline treatment group (19/21) comparing with the placebo group (2/9). Parents’ descriptions of their child’s behavioral improvements in this category included a decrease in maladaptive behaviors such as less fussing, crying, frustration, and tantrums and an increase in desired behaviors such as attention, independence, and purposeful actions. One parent stated, “His behavior is definitely getting better. The screaming has significantly decreased.” Another parent stated “he just isn’t as upset as much as he used to be.” Parents also noted that their child’s behavior did not improve. A parent stated, “He melts down sometimes but he just never stops.”

Approximately 89% of Behavior Improved (More) marked by an increase in attention, independence and purpose were observed in the sertraline treatment group (9/10). Out of 27 codes applied for Behavior Not Improved marked by either no change or increase in meltdowns, tantrums, and rigidity, approximately 70% (19/27) were found in the placebo group. Thirty percent of the codes applied for Behavior Not Improved belonged to the sertraline treatment group. The code Behavior Proactive Strategies was applied in seventeen excerpts. Of these seventeen, thirteen (76%) were applied to the placebo group and four (24%) were applied to the sertraline treatment group.

Communication

Of the twelve coded transcripts, communication related codes were identified most frequently (68/345) in our study. Communication related codes include Communication Improved Expressive, Communication Improved Receptive, and Communication Not Improved. The application of Communication Improved Expressive appeared 38 times
(56%) in the sertraline treatment group and 30 times (44%) in the placebo group.

Improvements in receptive communication emerged 12 times out of 17 in the sertraline treatment group, which comprises (70%) of the category. The code, *Communication Not Improved* was applied eight times and was distributed equally between sertraline treatment and placebo group (four in each group). The application of code *Communication Proactive Strategies* was found eight times in our data. A majority (6/8) of code *Communication Proactive Strategies* was applied in the placebo group. Parents’ descriptions of their child’s improvements in communication included changes in expressive and receptive language. For example, a transition was noted by a parent who stated, “He grabbed his bag because he thinks there's cheerios in there and that's something new he doesn’t do it that often.” When the researcher asked if this communication emerged in the last six months, the parent replied, “I think so, as I remembered it as it pronounced.” Another parent expressed:

> He's doing so much better. And then he...so I feel like he has done...it’s fun it’s a lot of fun to see the different words he will end up with and he will pop up with different words that we didn’t know that he would know he will just say things like “awesome.” Like you’re awesome, you’re awesome, and he will say “awesome.”

However, this study’s data also revealed communication that was not improved for some subjects. For example, one parent stated, “…but if not he gets upset he wants to get up he’ll absolutely bang his head against the board being bruised.” Another parent shared, “he doesn’t have control and he doesn’t know how to express it.” Our data shows that some children and
their families employed proactive strategies for communication as alternatives to verbal or nonverbal communication. For example, one parent explained:

So we use the sounding board app so he takes me to the one app, tells me what he wants, then gives this back to me… if he can’t say something he likes he knows he can go to the sounding board and then say it. Point to whatever it is that he wants and then you know [...] what he needs.

**Function**

Difference in functional improvement did not differ between the two groups. The same number of 19 applications of *Functional Improvement* was applied to both sertraline treatment (50%) and placebo group (50%). *Functional Not Improved* themes was found frequently in the placebo group, (16/18 times or 89%), comparing with 2/18 (11%) in the sertraline treatment group. Parents’ descriptions of their child’s functional improvements included activities of daily living and safety. One parent pointed out, “…now he's sitting, and he can attend to tasks. Like today, he put together 3 puzzles.” Another parent remarked his child is “…willing to try to get up and get on and actually play.”

**Community & Social**

Differences in community and social improvements were not found between the sertraline treatment and placebo groups. Out of the 18 applications of code *Community/ Social Improved*, eight were found in the sertraline treatment group and 10 were found in the placebo group. However, more non-improvements were coded in the placebo group, with seven out of eight applications (88%). Parents’ descriptions of their child’s improvements in the community
or in social environments included instances at the grocery store, parties, and family events. Such improvements are expressed by one parent in that:

He's been happier lately. I don't care what everyone says. He just has a lot happier moments and days. The report from school, all the teachers love him because he runs down the hall and he hugs them and the minute you sat down next to (him), you can get him to engage you right away. I think that's some difference with him.

In contrast, another parent noted that his child did not improve in community/social settings. He stated:

He still has a hard time when we walk into large crowds or groups or when people are coming at him. For example, we had a birthday party for his mom and we walked into the room and people getting him in the room first was like a feat because he knew that there was a lot of people. So he was like dragging his feet. He wanted to go the other direction. I picked him up and what he does is he will let us and pull our hair, grab our faces, and just pull.

Sensory

Sensory related code was found least frequently (18/345) across the transcripts. The code Sensory Improved (Less) was applied three times and came from the sertraline group. The application of Sensory Improved (More) was applied to four excerpts. Seventy-five percent of the Sensory Improved (More) codes were applied to the placebo group and 25% were applied to the sertraline treatment group. The application of Sensory Not Improved was applied to 11 excerpts. Seven out of 11 of these codes were applied to the placebo group and 4 out of eleven codes were applied to the sertraline group. Of the eighteen applications of the code Sensory Proactive
Strategies, eleven (61%) were applied to the placebo group and 7 (39%) were applied to the sertraline group.

Parents’ descriptions of their child’s improvements in sensory included an increase of desired responses to sensation such as more tolerance or more exploration of sensations or a decrease in maladaptive responses to sensation such as a decrease in self-stimulation, sensory-seeking, defensiveness, and avoidance. One parent stated, “I have been a lot better at, (wife) has too, about swinging him upside down and rubbing and massage him.”
Figure 2. Percentage of codes applied to the sertraline treatment and placebo groups.
Discussion

The research question that guided this study was: Can qualitative interview methods serve as an outcome measure capturing changes in occupational performance between treatment and placebo groups? Findings suggest that qualitative interview methods have good potential to serve as a supplemental outcome measure in a clinical trial. Interview methods provide opportunities for parents of children with FXS to describe changes in their child’s behavior, anxiety, communication, function, sensory processing, and social interaction within a holistic context which are less detectable by standardized norm-referenced assessments. Moreover, participation in a clinical trial has had an effect on both the child with FXS and their families’ ability to participate in their desired occupations.

The ability of parents to detect changes in their child’s expressive communication further prompts the necessity of interview methods as an outcome measure. For example, parents described that their children used gestures, such as pointing or hand-leading, which may be communication strategies that are less detectable in standardized tests. Furthermore, parents reported improvements in Behavior Less through decreased maladaptive behaviors in several daily contexts. This indicates that interviews can serve as an outcome measure as they capture a more detailed description of changes in day to day life, where standardized assessments are likely to focus on only one point in time.

Inconsistent results were reported within sensory improvements between Sensory Improved (More) and Sensory Improved (Less). All Sensory Improved (Less) improvements were found in the sertraline treatment group and the majority of Sensory Improved (More) improvements were found in the placebo group. Each parent, regardless of group assignment,
was given sensory proactive strategies by the occupational therapist to improve their child’s sensory processing. While the results were inconsistent, parents were still able to report the types of sensory strategies that were effective and strategies that were not, thus showing the importance of interview methods during a clinical trial as standardized assessments may not capture the types of strategies used and their effectiveness on sensory processing.

Improvements in community and social participation reflect an increase in the child’s participation in events such as going to the grocery store, park, family events, parties, and social interactions with peers, siblings, and adults. Hess et al.’s (2016) study showed that the sertraline treatment group had “nominal significant improvements in the social participation subscale raw score from the SPM-P” (p.7) and showed that families indicated positive changes in social aspects of daily routines. However, this study’s results indicated that the placebo group reported more improvements in community and social participation than the sertraline treatment group. As a whole, the participants’ ability to detect improvements in the community and with social interactions supports results from Tomlin and Swinth’s (2015) study which stated that incorporating semi-structured caregiver interviews can provide an occupation-centered lens to research studies examining living with FXS and its impact on family life.

Analysis of the semi-structured interviews with the codes defined in Table 1 revealed differences between the sertraline treatment and placebo groups in many areas. These results support the potential for interview methods to serve as outcome measures to capture changes in occupational performance between sertraline treatment and placebo groups in a clinical trial. These results are in line with Berry-Kravis et al.’s (2013) discussion of outcome measures in FXS noting standardized outcome measures lack sensitivity for IDD populations, prompting a
need for further outcome measures that are sensitive enough to small changes. This study was able to provide a qualitative measure that was effective in detecting changes in observable behaviors in children with FXS (Merriam, 2009).

The sociocultural theory and PEO model guided this research study. The sociocultural theory displays how differing social and cultural views affect both children with FXS and their families, and how those views can be useful in helping to understand FXS in a larger population (Vygotsky, 1978). The PEO model displays how environmental factors can have a great effect on how both the child with FXS and their families are able to participate in daily life (Law et al., 1996). These theoretical frameworks guided the data analysis as they helped researchers to focus on certain social and cultural interactions within the child’s environment and how those factors impacted the family’s daily life.

Data themes provided an in-depth, sociocultural and occupation-centered understanding of family perspectives in realistic and contextual situations within the larger bioecological framework of the sertraline clinical trial (Hess et al., 2016). Parents perspectives can help achieve a good fit between person, environment, and occupations to optimize performance (Law et al., 1996). Some personalized strategies to address behavioral, sensory processing, and anxiety needs were mentioned in the interviews. Environmental modifications, such as decreasing sensory input, packing bags with books and toys, and PECS, were helpful in managing some sensory processing, communication, and behavioral issues. In this way changing the child’s environment allowed for optimal occupational performance (Law et al., 1996).

As preliminary results from this study show, altering a part of the child’s biological process via medication has had an effect on the social and cultural interaction between children
with FXS, their families, and other individuals. For example, some children were able to participate in social settings, such as family events and even grocery shopping, which was less likely before participating in the clinical trial. Additionally, Vygotsky (1978) emphasized the dynamic systems in learning. As interactions with parents are crucial to the child’s development, the interview data can shed light on their communication methods, behavioral management approaches, sensory strategies, and adaptations in functional performance. Occupational therapists can take these perspectives into consideration when choosing a model to create treatment plans.

Implications for Occupational Therapy Practice

This study is important to the FXS community and to occupational therapy practice as functional participation in occupations is a crucial part to successful child development. Children with FXS have deficits in behavior, anxiety, sensory processing, and social participation that impact their families. Therefore, it is important for occupational therapists, as well as other disciplines, to guide treatment approaches for FXS with empirical research to address these issues. Using a top-down approach beginning with meaningful occupations to evaluate and treat the child, multidisciplinary teams should design evidence-based intervention strategies to promote greater occupational performance in children with FXS (Merriam, 2009; Portney & Watkins, 2015). The use of family perspectives will enrich therapists’ understanding of the lived experience of FXS, which can further help guide occupation-based, client-centered intervention and give meaningful outcomes for children and their families.
Limitations and Future Directions

This research has limitations that should be considered. Firstly, researchers did not create “mother” codes such as behavior improved or communication improved for excerpts that did not specify which area the improvement occurred (more or less, receptive or expressive); creating a general code would have prevented researchers from having to assign two codes, or no code at all, to the excerpts. Another limitation is that member checks were not possible as the original sertraline study had been completed prior to this analysis. Finally, this study only examined the post-interview.

Future studies may examine the remaining questions in the interview protocol to gather additional information about the parents’ thoughts of the clinical trial and their hopes of the research in order to add a holistic, family-centered approach. Our data reported frequency of code applications in percentages. Future research with additional data may be able to compare groups with more robust statistical analyses. Additionally, future research may consider a comparison analysis between the baseline interview and the post-testing interview of each subject for a case-based thorough analysis. This will help therapists gain insight into how parents saw their children before the clinical trial and what aspects of their child’s behaviors and disability concern them most.

Conclusion

FXS is the most common form of inherited IDD and the most common single gene cause of ASD. The behavioral phenotype includes cognitive impairments, SIB, anxiety, global language delays, sensory processing deficits, and decreased social participation. These behaviors
not only affect the children with FXS, but their families as well. To date, research literature has focused primarily on quantitative methods and the medical model. While standardized and norm-referenced assessments and parent checklists are widely used as outcome measures, their ability to detect contextually-based change is limited. The addition of supplemental, semi-structured interviews revealed differences between sertraline treatment and placebo groups in many coded areas in this sample.

This study examined family interview data collected from a FXS clinical trial at the UC Davis MIND Institute (Hess et al., 2016) to measure the potential for family reports to serve as a qualitative outcome measure. The results support the potential for interview methods to serve as an outcome measure when used in conjunction with standardized and norm-referenced assessments and parent checklists in a clinical trial. Similarly, these results indicated that interview methods show potential to identify contextually-based differences between the treatment and placebo groups in a clinical trial. The addition of qualitative interview methods can provide family voice and personal stories and an occupation-centered lens. Our research also revealed the feelings of altruism that families experienced through participating in the clinical trial at the UC MIND Institute (Hess et al., 2016). Families in both sertraline treatment and placebo groups reported that regardless of the outcome of the clinical trial, they hoped that knowledge gained from this study may inform scientific research and its consumers, and ultimately benefit future generations of children with FXS and their families.
Acknowledgements

The researchers would like to sincerely thank the UC Davis MIND Institute and families in the FXS community who contributed to this research. This study was funded by Health Resources and Services Administration (HRSA, #R40MC22641).
References


Interview Protocol – Sertraline
Annual Review (June, 2013)

The interviews will be conducted either at the MIND Institute or via phone with a MIND FXS research clinician. Interviews will be conducted in a conversation format, audio recorded and transcribed for qualitative coding of the interview data. All personal information will remain confidential and pseudonyms will be used. The following questions will structure the overall interviews, yet, because the interview process is based on emergent responses, probes and follow up questions may be added as appropriate to clarify or expand upon responses provided by the interviewees. The interviews should average 30-45 minutes in length.

### Baseline

The purpose of the interview is to gain insight into family perspectives from their point of view, in their own words, regarding issues surrounding participating in a clinical trial with a 2-6 year old child diagnosed with FXS. Please share stories, anecdotes and “for examples” as they come to mind as these rich descriptions are very meaningful and important to our research.

1. Tell me about (child’s name). I realize we are all here at the MIND for specific clinical / research reasons, but I want to back up and talk about your child as a little person who has strengths, gifts and talents. I especially want to hear stories about the kinds of things you enjoy about (child’s name).

2. Tell me about your child’s activity level / behavior? How do you feel anxiety may or may not play a part in behavior? Tell me a story about how this may impact you as a family?

3. What do you notice about your child’s reactions to sensory input? (moving through space, sound, touch, smelling things, eating). Tell me a story about how this may impact you as a family?

### 6 month appointment – prior to family “unblinding”

During our first interview we were able to discuss your child’s strengths and patterns including behavior, sensory, anxiety and communication and the impact on your family. As a follow up to that conversation, today I would like us to discuss any changes you have seen since beginning the study in these areas and the impact to your family. Again, please share stories, anecdotes and “for examples” as they come to mind as these rich descriptions are very meaningful and important to our research.

1. Let’s start with activity level and behavior. What changes if any have you noticed and how has that impacted you as a family.

2. Have you noticed any changes related to anxiety? How has that impacted you as a family?

3. Have you noticed any changes related to sensory processing? How has that impacted you as a family?

4. Have you noticed any changes related to communication? How has that impacted you as a family?

5. Do you think you were given the placebo or the medication? What were you observing / feeling that has led you to wonder whether you had the medication or not?
4. Tell me about your child’s abilities in **communicating** with you? Other family members? Other children? Tell me a story about how this may impact you as a family?

***5. What interventions are you **participating in** currently including school and/or therapies (such as OT / speech)? Is there anything you would like to see changed about your child’s intervention situation or the way he or she is during intervention / services?

6. **What has led you to participate in research that includes a trial of medication?**

7. Tell me your feelings about the possibility that your child may get the real medication? Tell me your feelings about the possibility that your child may get the placebo?

8. What are your expectations and/or **hopes for this research study for your family in particular**? What does participating in this type of research mean to you and your family?

9. Is there anything you would like to share in terms of your family’s involvement in the research study regarding what you have learned thus far and what your hopes are for overall or big picture learning that can come out of the research?

6. Is there anything you would like to share in terms of your family’s involvement in the research study regarding what you have learned thus far and what your hopes are for overall or big picture learning that can come out of the research?