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April 16, 2013

Targeted Clinical Drug Trials for Intellectual Disabilities: The Decision-Making Process

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a thesis submitted to the Faculty of Emory College of Arts and Sciences  
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## Abstract

### Targeted Clinical Drug Trials for Intellectual Disabilities: The Decision-Making Process

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**Background.** Research and literature has addressed parental decision-making when it comes to prenatal diagnosis for fetuses with genetic conditions resulting in intellectual disabilities. The recent advent of targeted drug trials for intellectual disabilities poses questions about decision-making in the post-natal period and throughout the life span of this vulnerable population that have not yet been explored. **Objective.** To explore this uncharted territory, we examined factors that influence parental decisions to involve children in a clinical drug trial for Fragile X Syndrome or Down Syndrome. **Methods.** IRB approval was obtained and 24 parents of individuals with Fragile X Syndrome or Down Syndrome participated in phone interviews. We asked about child involvement in trials and attitudes towards trials and medication. We hypothesized that parents of children with Fragile X Syndrome or Down Syndrome who are more severely affected with debilitating behavioral problems are more inclined to explore or take an interest in clinical drug trial enrollment for their child. **Results.** We found no evidence for a correlation between a child's behavioral problems or the parent's perception of the child's overall health and a parent's interest in drug trials. Generally, parents were more willing to involve their child in a decision for him/her to take a lifelong medication than to participate in a trial. **Limitations.** Our participants may not be representative of the target population. Recruitment was primarily done through an academic medical institution so most participants had knowledge or involvement in research. Drug trials for Down Syndrome are new and involve individuals between the ages of 18 and 30; thus, it was difficult to find participants with a child who has been involved in a trial for Down Syndrome. **Conclusions.** Some of the factors influencing the clinical drug trial and treatment decision-making of this population include: child's behavioral problems, parental attitudes towards drug trials, parental attitudes

towards medication, hopes for improvement, concerns, child involvement, and misunderstandings about trials.

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## **Introduction**

Daily life has been altered by devices, such as mp3 players, ipods, iphones, and voice recorders. These, and other advancements have been beneficial and increased the ease of certain activities; however, technology and research have also complicated aspects of society. Healthcare is one facet of society that has seen beneficial technological developments such as stem cell research, life-prolonging technologies, conception techniques, and drug research. Such developments have changed medicine significantly. For example, they have allowed individuals previously unable to conceive to have children. Advances have prolonged life via dialysis, a respirator, or other medical equipment. However, “the advances of modern medical science have created a whole new spectrum of decisions that we may prefer not to make, but there is no escaping our duty to confront these issues as responsibly as we can.”<sup>1p.131)</sup> Dilemmas surrounding the issue of when life actually begins, when it is acceptable to alter life, when life should be prolonged, and when technology should step aside and allow death to be ‘natural’, bring difficulty to the use of new technology. Bioethics is the growing field that addresses such concerns. As technological advancements are made, America reforms healthcare, and research paves the way for new drug development, bioethics is an essential field to address ethical questions related to policy and implementation. This paper will specifically focus on the intersection of genetics and ethics as it relates to decision-making for, or by, a “vulnerable” population, those with intellectual disabilities. This project will focus on experimentation and treatment. It will explore the ways in which decisions are made for individuals who have genetic disorders limiting their cognitive abilities. To begin surveying this broad subject, this paper will use two case studies: Fragile X Syndrome (FXS) and Down Syndrome (DS). We will address decision-making related to treatment and clinical trial participation of individuals with these intellectual and developmental disorders. Research and literature have explored ethics and decision-making of clinical drug trials, studies which will be further explored in the discussion, however because targeted therapies for intellectual disabilities are so new, ethical considerations, specifically the decision-making aspect, of such trials have yet to be explored. This paper will focus on recent research, as well as

this unexplored area of bioethics. We will begin by reviewing previous research on genetics and ethics, the biology of FXS and DS, new research on these disorders, and a brief overview of clinical drug trials.

### ***Bioethical Research on Prenatal Diagnosis and Termination Decisions***

In 1978, the first child conceived in an *in vitro* environment was born.<sup>2</sup> This tremendous medical breakthrough allowed individuals previously unable to conceive naturally, to have children. Further, such developments allowed the screening of embryos for possible disease: preimplantation genetic screening and diagnosis (PGD) allowed embryos conceived in an *in vitro* environment to be screened before insertion into a woman's uterus for growth and development.<sup>2</sup> In other words, embryos could be tested for inherited genetic disorders before implantation. This development would avoid ethical dilemmas surrounding pregnancy termination, because screening would occur before pregnancy.<sup>3</sup> Prior to PGD, any screening and diagnosis occurred during pregnancy, and the only way to prevent the birth of an individual with a certain phenotype was to terminate the pregnancy, forcing the parents to make a difficult decision.

Unfortunately, PGD is not completely without ethical concerns. Primarily, opponents have concerns about future applications.<sup>4</sup> Because PGD allows sex-determination of the embryo, an important component when diagnosing an X-linked genetic disorder,<sup>3</sup> there is some fear that PGD will be used solely for sex-selection.<sup>4</sup> Dahl also mentions that PGD could also be used to select for characteristics such as height, cognitive function and sexual orientation.<sup>5</sup> Although this is not feasible due to the complexity of the genetic architecture of these complex traits, they are put forth as issues that might provoke ethical qualms. More imminent are concerns surrounding the current applications of PGD, many of which are similar to ethical concerns about selectively aborting fetuses. New technology and research allowing life to begin in new ways has inevitably presented more and new possibilities and decisions parents must make when it comes to their reproductive options. Current literature addresses prenatal parental decision-making and the ethical considerations at play, including whether a fetus is an individual

with rights, and whether termination of an embryo before implantation and viability is morally permissible.<sup>6</sup> Opponents of prenatal screening and diagnosis have argued that these recent developments pose ethical problems because they force parents to decide whether to abort a conceptus; thus, some suggest that they should be prohibited.<sup>6</sup> Notably, prenatal screening and diagnosis give parents information that they otherwise would not have; in the case of a positive screen or diagnosis, this new information forces the parents to decide whether to continue the pregnancy, or terminate the conceptus.<sup>7</sup>

Furthermore, opponents of selective abortion for certain genetic disorders argue that “if prenatal diagnosis is used as a tool to eradicate as many disabilities as possible in society, then it... discriminate[s] against people with disabilities.”<sup>8(p.165)</sup> Research that focuses solely on the ethics of prenatal decision-making might corroborate this view. Alternatively, research on the ethics of decision-making related to care and treatment of individuals with certain genetic disorders after birth could challenge that argument and lead to increased quality of life for those with genetic disorders. Perhaps this could dismantle existing stigma against disabilities. Despite abundant literature on the ethics of decision-making related to diagnosing and selectively terminating fetuses with a genetic disorder, we are not aware of literature addressing decision-making of treating, and experimenting on individuals with intellectual disabilities, most likely because targeted drug trials for intellectual disabilities are only very recently being attempted. Further, recent drug development has targeted the disease pathways of FXS and DS, instead of simply targeting symptoms of the disease.<sup>9</sup> Should an individual with an intellectual disability, for example FXS, who is unable to fully comprehend their disorder or understand the safety or efficacy of a drug, make a decision to take medication and/or to enroll in a clinical drug trial? Related, is this decision solely the parents’ responsibility? Most importantly, when is a child with an intellectual disability considered competent to make a decision? And who should evaluate that individual’s competency? This project will explore these questions.

FXS and DS provide excellent case studies on parental decision-making for those with intellectual disabilities. Häyry et al discuss the importance of competence and capacity: “being competent

or having capacity is a necessary ability for understanding the relevant information about different possible interventions, and for making the decision about which option to adopt.”<sup>10(p.94)</sup> Individuals with FXS and DS can have limited decisional capacity because their intellectual development limits understanding and reasoning. Thus, individuals with these disorders rely on a surrogate decision-maker.

### ***Fragile X Syndrome***

#### *Description of the disorder and its genetic etiology*

FXS is seen in 1 out of 4000 males and 1 out of 4000 to 8000 females.<sup>11</sup> FXS is typically associated with problems with language, intellectual development, and behavior.<sup>12</sup> The physical features can include characteristic ears, a narrow face, and, among males, abnormally large testicles.<sup>12</sup> FXS is inherited as an X-linked trait.<sup>12</sup> Because this genetic disorder is carried on the X-chromosome, males are more severely affected than females, as females have two X-chromosomes, one of which can mask the fragile X mutation, while males have only one X-chromosome. The inherited mutation is due to an expanded trinucleotide repeat, cytosine-guanosine-guanosine (CGG), in the 5' untranslated region of the *FMR1* (Fragile X Mental Retardation) gene; expansions of 200 CGG repeats or greater lead to abnormal hypermethylation of the repeats and the surrounding regulatory region.<sup>12</sup> As a consequence, the *FMR1* gene is silenced.<sup>12</sup> Thus, this full mutation leads to the absence of the fragile X mental retardation protein (FMRP). Individuals with 55 – 200 CGG repeats are classified as premutation carriers; in this case, the repeats are not methylated and FMRP is unaffected.<sup>12</sup> FMRP affects synaptic transmission, which is important for learning and memory.<sup>13</sup> Thus, the absence, or a reduction of FMRP, the gene product of *FMR1*, can affect intellectual development.

The unusual inheritance of FXS is related to the unique features of the X-linked repeat mutation.<sup>12</sup> Like all X-linked traits, there is a 50% chance that a mother with the mutation will pass it on to her child, because each child inherits one X-chromosome from his/her mother. If a father carries the mutation, he will definitely pass it on to all of his daughters, because every female child inherits one X-chromosome

from their father, while none of his sons will inherit the mutation as every male child inherits only a Y-chromosome from his father.

The characteristics of the expansion of the premutation to the full mutation overlay the X-linked pattern. This expansion depends on the repeat length of the premutation and on the sex of the parent who is transmitting that permutation.<sup>14</sup> As the premutation repeat length increases, the risk that it expands to the full mutation increases. Also, the expansion to the full mutation only occurs when transmitted by the mother.<sup>14</sup> Thus, all children with the full mutation, those who express FXS, have inherited the mutation from their mothers.

#### Targeted drug research to treat fragile X syndrome

As mentioned, new drugs that have been recently developed target the molecular consequence of the absence of FMRP, rather than trying to ameliorate symptoms associated with FXS. Studying the etiology and biochemistry of FXS has the potential to provide information important for treating other types of intellectual disabilities, because this inherited mutation causes autism spectrum disorders.<sup>15</sup>

The work of Huber et al in 2002 with Fmr1-knockout mice introduced the mGluR theory of FXS, predicting that features of FXS could result from increased group I metabotropic glutamate receptor (mGluR1/5) activation resulting from the absence of FMRP.<sup>16</sup> These researchers showed that Fmr1-knockout mice had abnormally high levels of GluR1/5-mediated long-term depression (LTD), involved with synaptic plasticity, in the hippocampus.<sup>16</sup> This process allows the circuitry of the nervous system to be sculpted and to fine tune individual synaptic contacts, indirectly affecting learning and memory. Huber et al found that mGluR1 and mGluR5 activation is associated with proper LTD.<sup>16</sup> Thus, Huber et al hypothesized that the connection between reduced FMRP levels and increased mGluR activation could affect learning and memory via altered synaptic activity.<sup>16</sup> Further work with Fmr1-knockout mice showed that FMRP inhibits translation of proteins involved in stabilizing LTD; based on these findings, researchers have explored the use of mGluR antagonists as a therapy for FXS as a way to prevent continued activation of mGLuRs that leads to increased LTD.<sup>16</sup>

An additional area of research has focused on connecting a loss of FMRP with fewer gamma amino-butyric acid (GABA) receptors has also been enlightening because of GABA's role as an inhibitory neurotransmitter.<sup>9</sup> Fewer GABA receptors means there is a decreased opportunity for GABA to bind to the receptors and function as an inhibitory transmitter. Similar to the findings associating FMRP and mGluRs, researchers have taken advantage of these new findings about GABA receptors to develop potential targeted therapy for individuals with FXS. Thus, GABA agonists, such as Arbaclofen,<sup>9</sup> have been developed to increase GABA activity.

### ***Down Syndrome***

#### *Description of the disorder and its genetic etiology*

Similar to FXS, DS is a genetic condition affecting intellectual development, and thus can impair decision-making capacity. New research has also allowed more targeted drug development and treatment of DS, as oppose to drugs treating general symptoms of DS. DS, or trisomy 21, is a genetic disorder in which a child is born with three copies of chromosome 21. DS occurs in 1 in 600 babies in the United States.<sup>17</sup> Clinically, DS is often associated with distinctive facial features and hypotonia.<sup>18</sup> Although almost all of individuals with DS have intellectual disabilities, there is a wide range of function.<sup>17</sup> Behavior and speech problems are common in individuals with DS.<sup>17,18</sup> Also, a proportion of individuals with DS are at risk for congenital heart defect, gastrointestinal defects and later onset disorders such as childhood leukemia, obesity, celiac disease, hypothyroidism and Alzheimer disease.<sup>17,19</sup>

The majority of cases of DS are not inherited. In about 95% of individuals, DS results from nondisjunction, a chromosomal error that occurs during the formation of egg or sperm; the remaining cases are due to chromosomal translocations or to a post-zygotic chromosome error.<sup>19</sup> About 1% of cases are mosaic, where an individual has an extra chromosome 21 in only a proportion of cells. On average, individuals who are mosaic for trisomy 21 have milder symptoms of DS than those with standard trisomy 21.<sup>20</sup> However, there is a wide range of abilities among all individuals with DS.

Meiosis is the process of cell divisions during the formation of gametes that are necessary for reproduction and the passage of genetic information to future generations. For each human cell to have the correct, 23 pairs of chromosomes, chromosome segregation must occur in a specific way during meiosis. Nondisjunction occurs when chromosomal segregation is asymmetric and daughter cells receive an abnormal number of chromosomes or chromatids.<sup>21</sup> Fertilization of a gamete with too many or too few chromosomes leads to an aneuploid conceptus.<sup>19</sup> The majority of aneuploid conceptuses spontaneously abort; however, DS is a trisomy that can survive to term, although those surviving only represent about 20% of trisomy 21 conceptuses.<sup>19</sup> The most important risk factor for nondisjunction is advanced maternal age: as the age of the woman, or more precisely her oocyte, increases, the risk for nondisjunction increases.<sup>19</sup> This is most likely due to the fact that an oocyte begins meiosis I during embryonic development and remains arrested in prophase I until that oocyte is ovulated some 10 to 40 years later.<sup>19</sup> The 4% of trisomy 21 births are due to a chromosome translocation,<sup>18</sup> or an attachment of genetic material to a different location in the genome.

#### Targeted drug research to treat Down syndrome

Recent drug development and research have attempted to target the biochemical processes that result from trisomy 21. The presence of an extra chromosome 21 (or in some cases of Down syndrome, an extra copy of some sections of chromosome 21) results in increased expression of genes on the triplicated portion of the chromosome. Recent research initiatives studied trisomic mice to highlight potential treatment techniques targeting the underlying biochemistry of trisomy 21 in humans. One study looked at different sections of chromosome 21 to determine whether particular aneuploid sections of chromosome 21 alone could cause Down Syndrome.<sup>22</sup> To determine this, researchers used genetically engineered mice that were triploid for different portions of chromosome 21, to examine the effects of overexpression of genes in specific regions; they first looked at the Down Syndrome Critical Region (DSCR).<sup>22</sup> Researchers used a DS mouse model that carries close to half of a third chromosome 21 (Ts65DN), which showed craniofacial structural anomalies and another mouse model, with only the



triplicated DSCR, which did not exhibit the phenotype distinguishable in Ts65DN mice.<sup>22</sup> Taken together, this study implied that a triplicated DSCR alone does not result in facial abnormalities.<sup>22</sup>

The researchers then used these same models to examine hippocampal activity as assessed by the Morris water maze (MWM), testing the ability of an animal to learn using navigation from visual signals.<sup>22</sup> The Ts65DN genotype exhibited low functioning, while the Ts1Rh and Ms1Rhr/Ts65Dn (a Ts65DN mouse without a triplicated DSCR) genotypes exhibited the same abilities as wild-type (WT) (those with two copies of chromosome 21).<sup>22</sup> These results implied that trisomy for the DSCR is necessary to produce this specific hippocampal deficit.<sup>22</sup> This research is important in determining the significance of the DSCR and how overexpression of certain portions of chromosome 21 might influence the Down syndrome phenotype.

Another study explored how the disruption of cell-cell communication might be responsible for the aforementioned 'hippocampal disruption'. Similar to the biochemistry behind FXS, LTD is thought to play a role in cognitive impairment associated with DS.<sup>22</sup> Because increased GABA neurotransmitter activity is thought to increase LTD, the use of GABA receptor antagonists was explored.<sup>22</sup> Dr. Craig Garner studied possible antagonists of this receptor, including picrotoxin (PTX), bilobalide (BB), and pentylentetrazole (PTZ) which all seemed to improve the memory of the Ts65Dn mice to a level comparable to the WT mice.<sup>22</sup> Such results support the role of GABA in memory and hippocampal activity.

### ***Clinical Drug Trials***

While remarkable new research on therapy targeting intellectual disabilities is underway, before new drugs are put on the market, extensive drug trials must be done to test the safety and efficacy of new treatment options. Highly unethical drug trials in the past have encouraged the creation of Institutional Review Boards to impose strict regulations to ensure that subjects are treated with dignity and respect. Such past experiences include Nazi experimentation on Jews during World War II, and the Tuskegee

Syphilis trials where penicillin, a known treatment for Syphilis, was withheld from subjects.<sup>23</sup> The zidovudine (AZT) international trials to survey the efficacy of AZT in inhibiting the transmission of HIV/AIDS from mother to child have also raised ethical concerns.<sup>24</sup> The researchers in this trial used a population of international pregnant women to test the effectiveness of a reduced dose of the drug by comparing it to a placebo.<sup>24</sup> Ethical concerns arose during this study in part because research was being done on individuals in third-world countries to compare a reduced dose of a medication, which was less than the U.S standard of care, to no medication at all.<sup>24</sup>

Because of certain experimentation and drug trials that have happened in the past, strict regulations have been developed to help ensure that drug trials are performed ethically. In 1978, the *Belmont Report*, was published by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, to address drug trial regulation.<sup>25</sup> This comprehensive document discusses the principles of bioethics: respect for persons, or autonomy, beneficence, sometimes referred to as non-maleficence, and justice, as well as different procedures, such as informed consent, integral to the drug trial process.<sup>25</sup> These principles and procedures will be later addressed in the context of this study. The sections of this document addressing Respect for Persons, and Informed Consent, both address the idea of capability, and individuals who are and are not ‘capable’ of making an autonomous decision with respect to drug trials. The report explains that “an autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation...However, not every human being is capable of self-determination...some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty.”<sup>25(p.5)</sup> This document has become vital for clarifying procedures that must be enforced in order to engage in drug trials with human subjects, especially since there have been questionable studies raising ethical concerns about the use of human subjects in such trials.

This report explored the idea of ‘capability’ in decision-making. Decision-making is critical when it comes to participation in drug trials. This precaution is especially important for individuals who are

intellectually and developmentally challenged, and may be unable to make a competent decision. We studied FXS and DS as examples of two genetic disorders that impair cognition and thus can affect decision-making capability as it is described in *The Belmont Report*. We surveyed the process and ways in which a parent makes the decision for his/her child to enroll, or not enroll, in a clinical drug trial. We also probed how much, if at all, the parents can, and do, involve their children in the decision. We hypothesized that parents of children with FXS or DS who are more severely affected with debilitating behavioral problems are more inclined to explore or take an interest in clinical drug trial enrollment for their child.

## **Methods**

### ***Molecular Laboratory Shadowing***

During my time shadowing Lab Technicians in the Emory Genetics Molecular Laboratory, I had the opportunity to observe an Asuragen PCR Assay as part of the FXS diagnosis assay. This new technology provides information to accurately assess CGG repeat's length located in the 5' UTR of the *FMRI* gene that are in the pre and full mutation range. Endnotes refer to protocols used in the lab.

*Asuragen PCR Assay*<sup>26</sup>

*Methylation Sensitive Polymerase-Chain Reaction (PCR) Analysis*<sup>27</sup>

*Southern Blot*<sup>28</sup>

### ***Cytogenetics Laboratory Shadowing***

During my time shadowing in the Emory Cytogenetics Laboratory, I had the opportunity to observe Lab Technicians perform various assays and tests used to diagnosis DS, including a karyotype, fluorescence in situ hybridization, and a comparative genomic hybridization microarray. Endnotes refer to protocols used in the lab.

Karyotype<sup>29</sup>

Fluorescence in situ hybridization<sup>30</sup>

Comparative Genomic Hybridization Microarray<sup>31</sup>

### **Original Research: Data Collection**

#### Subjects:

Approval for the study was obtained by the Emory University Institutional Review Board. Twenty-four subjects were interviewed and included nine parents of individuals with FXS and 15 parents of individuals with DS. Some of their children were involved in clinical drug trials, others were not. Participants were recruited from Emory's Fragile X Syndrome and Down Syndrome centers, including the clinics and research centers. A recruitment flyer was also sent to the Georgia LINKS group, which is sponsored by the National Fragile X Foundation. Contact with participants was made via email and a consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization information sheet were sent to each participant. Once the participant agreed to participate, a phone interview was scheduled.

#### Phone Interviews:

Each phone interview was recorded, and verbal consent and HIPAA authorization consent were obtained. A short demographic survey preceded the interview. An interview guide was used to conduct the semi-structured interview, which asked questions about the participant's child as well as their thoughts on clinical drug trials.

#### Data Collection and Analysis:

The recorded interviews were transcribed using Dragon Dictation Software. Any names mentioned during the interview, and all identifiers were removed from the transcription prior to analysis. All notes, recorded interviews and transcriptions were saved and backed up on an encrypted hard drive.

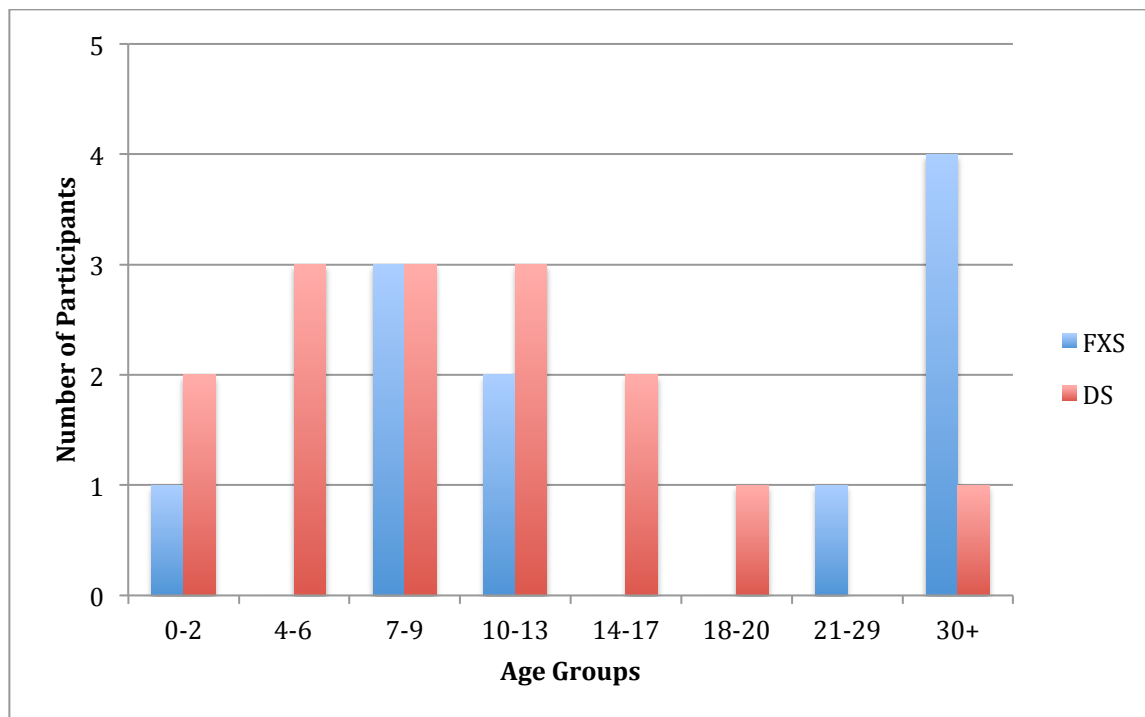
Three members of the research team read through one FXS transcription and one DS transcription independently. Then, they met to discuss the initial coding and to define codes, creating a codebook. The remaining transcriptions were independently coded by two members of the research team, and discussed to corroborate consistency and consensus of codes.

Comments made by subjects are included in the results section and parenthetically reference the subject's study number and the child's condition, for example (F22) would refer to a comment made by participant 22 who has a child with Fragile X Syndrome.

## **Results**

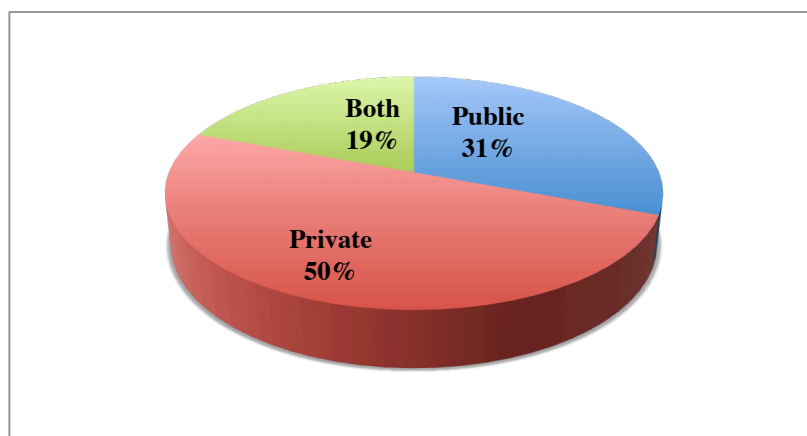
### ***Demographics***

Twenty-four parents were interviewed, consisting of 22 mothers, and two fathers. Two mothers each had two children with FXS, but all other subjects had one child with either FXS or DS. Nine subjects had a child (or children) with FXS, and 15 subjects each had one child with DS. Eleven of the children with DS were males, and nine of the children with FXS were males. The ages of the children are illustrated in Figure 1.

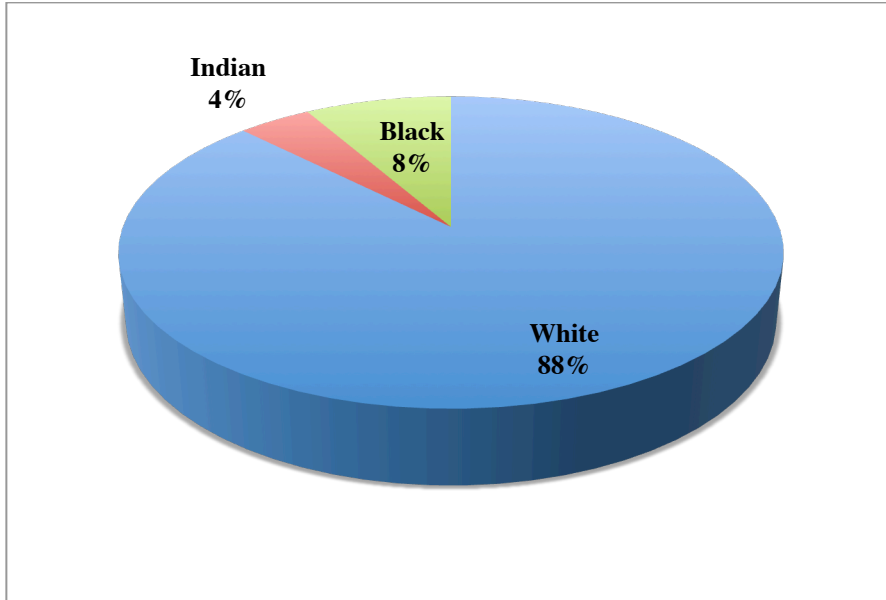


**Figure 1: Ages of Children of Subjects**

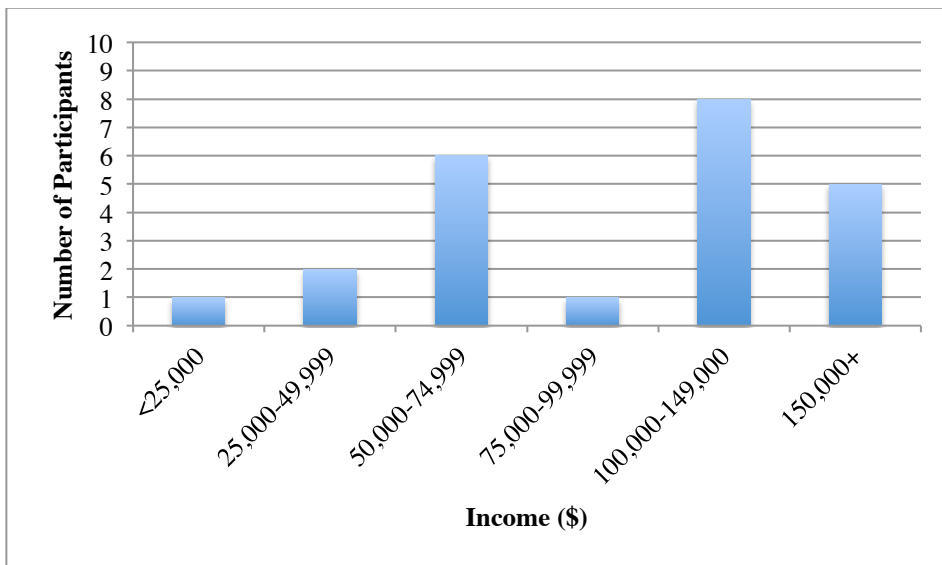
The breakdown of parents by other demographics is illustrated in the following graphs: insurance status for their child (private health insurance, public health insurance, or both (Figure 2)); race/ethnicity of parents (Figure 3); parents' household income levels before taxes (Figure 4); and, highest level of education completed (Figure 5)). Also, 21 participants were married, one was single, one was widowed, and one was living with her partner.



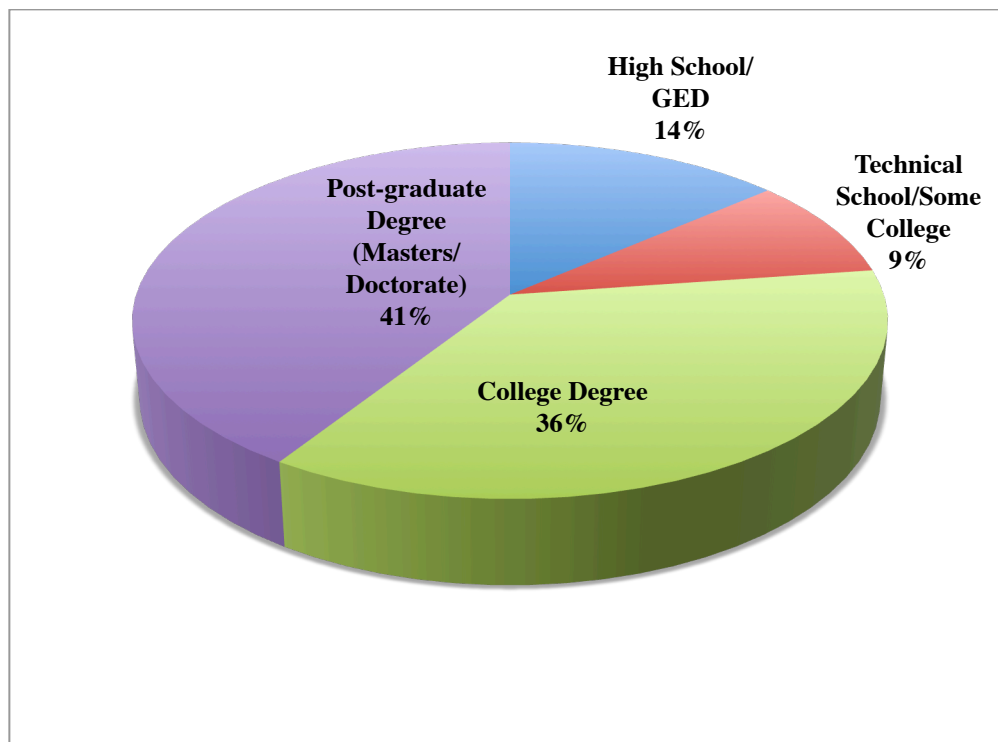
**Figure 2: Type of Children's Health Insurance**



**Figure 3: Races of Participants**



**Figure 4: Family Household Income**

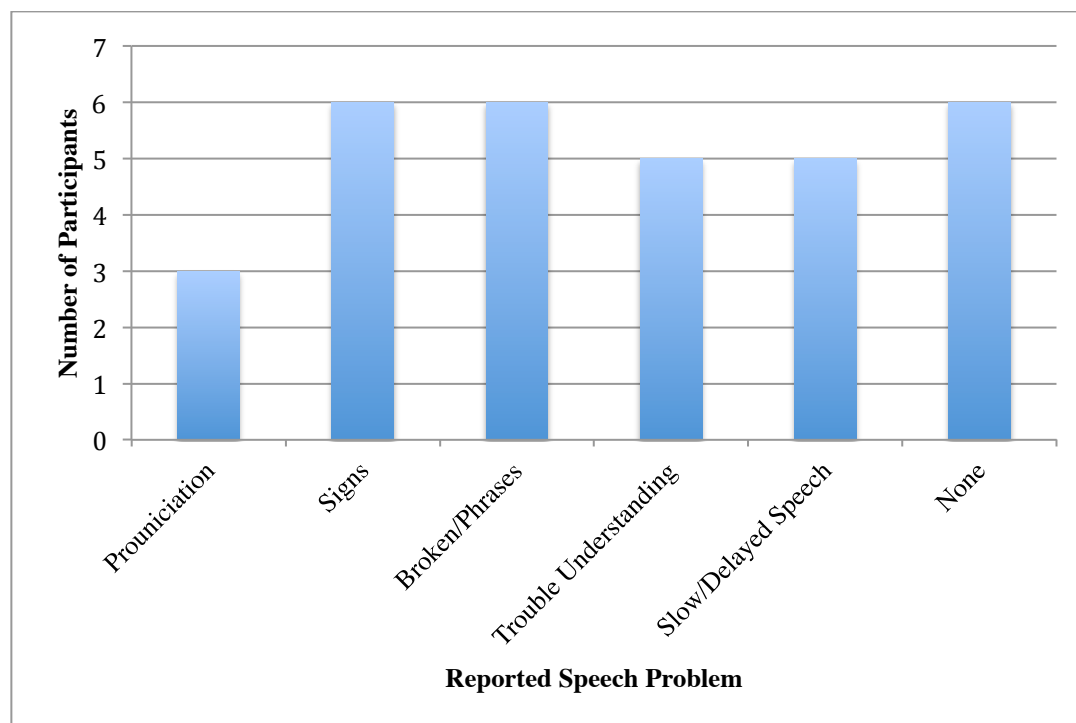


**Figure 5: Subjects' Highest Level of Education Completed**

### *Health of the Child*

Parents were asked several questions related to the health of their child: 1) whether their child(ren) exhibited any communication, behavioral, or medical problems, 2) to describe the overall health and well-being of the child, and 3) to state whether their child(ren) might be taking any medication. Of the subjects who have children with FXS, six of the nine perceived their child(ren) to have problems with communication, and of those who have children with DS, 12 of 15 perceived their child to have problems communicating. Problems with communication are illustrated in Figure 6. Parents typically described their children as having more than one of the problems illustrated in Figure 6.



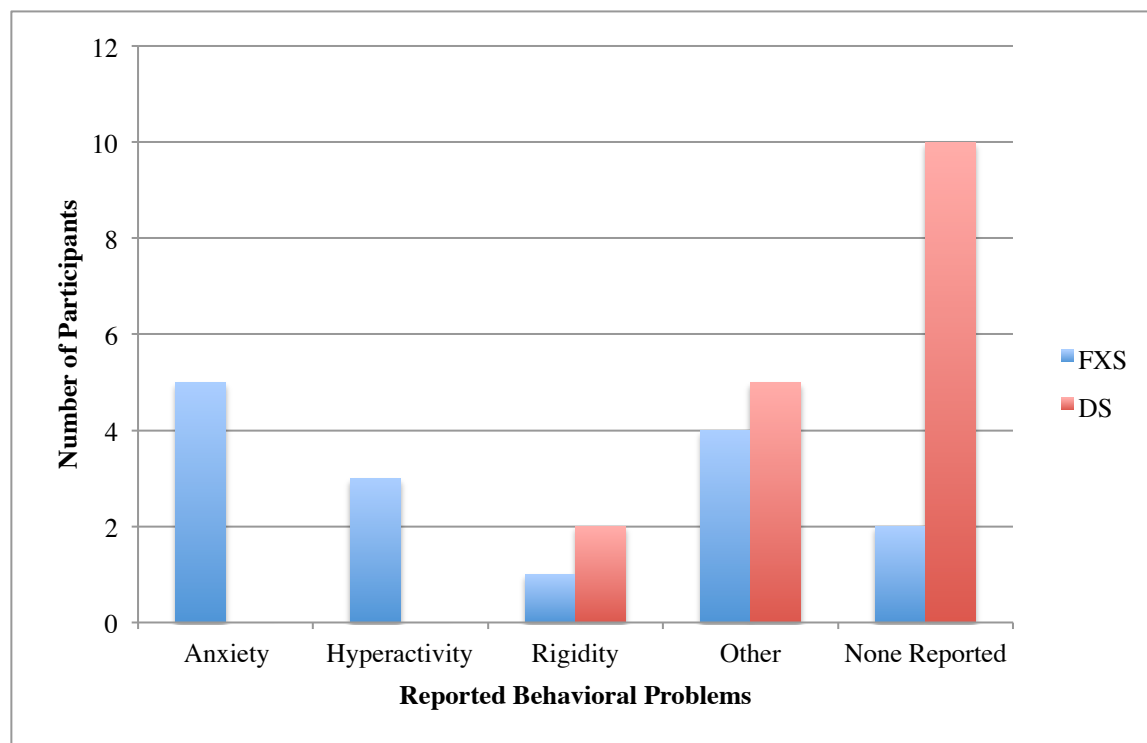


**Figure 6: Types of Speech and Communication Problems Reported**

One parent explained that her son “has typical DS speech which is sometimes difficult to understand because of the shape of his tongue and the placement, and I’m a former speech therapist. But it is difficult. He is generally able to communicate but he’s not always understood easily.” (D8) Another parent explained, “[my daughter] is difficult to understand, the sound of the words as well as, she has, I’m not sure what it’s called exactly, but stuttering on some words so it’s hard for her to produce fluid speech. The rest of us understand her but strangers sometimes don’t have the patience to.” (D5)

Seven of the nine subjects with children with FXS perceived their child(ren) as having behavioral problems, and five of the 15 parents of individuals with DS perceived their child as having behavioral problems. Parents frequently mentioned they their children exhibited multiple problems. The specific behavioral problems are detailed in Figure 7 by genetic disorder. One parent explained that, “because [my

son] has fragile X, he pretty much has a lot of anxiety and a lot of defensiveness. He has a lot of transitional issues so that ... causes him to have challenges.” (F18)



**Figure 7: Behavioral Problems Reported**

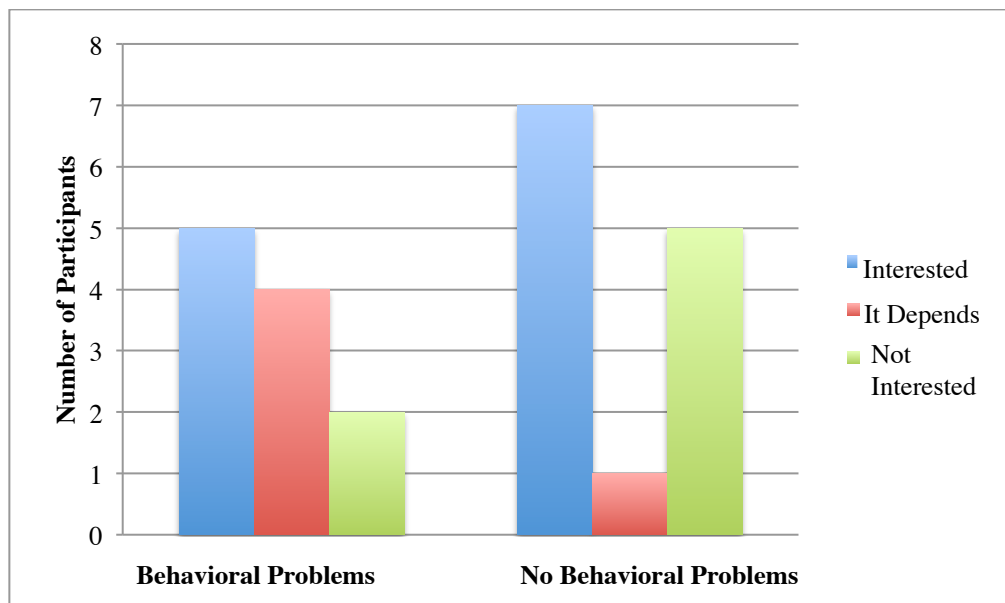
In response to being asked about major medical problems, 20 participants explained that their child(ren) had none, while four parents of individuals with DS described medical problems including, heart problems, hypothyroidism, diabetes, Celiac disease, and reflux. Twelve parents said that their child(ren) takes no medication while others mentioned Ritalin, Vyvanse, insulin, Risperdal, Strattera, Zoloft, Trileptal, guanfacine, thyroid medication, reflux medication, and one parent described supplements including fish oil, and folic acid.

In response to being asked whether or not subjects perceived their child(ren) to be doing well and in good health, 21 responded ‘absolutely yes’, while three parents were hesitant to say yes, or questioned the term “good health”. One of these three explained:

She is doing well, but, I mean we haven't been in the hospital this year. But good health? How do you decide on good health yeah know what I mean? ... We didn't go to the hospital, well that's good at least...But is it good? Well compared to what? Everybody else? No. Compared to her little girlfriend, her little bestie with Down Syndrome? Absolutely. She gets a cold, she's in the hospital every time. So compared to what? (D9)

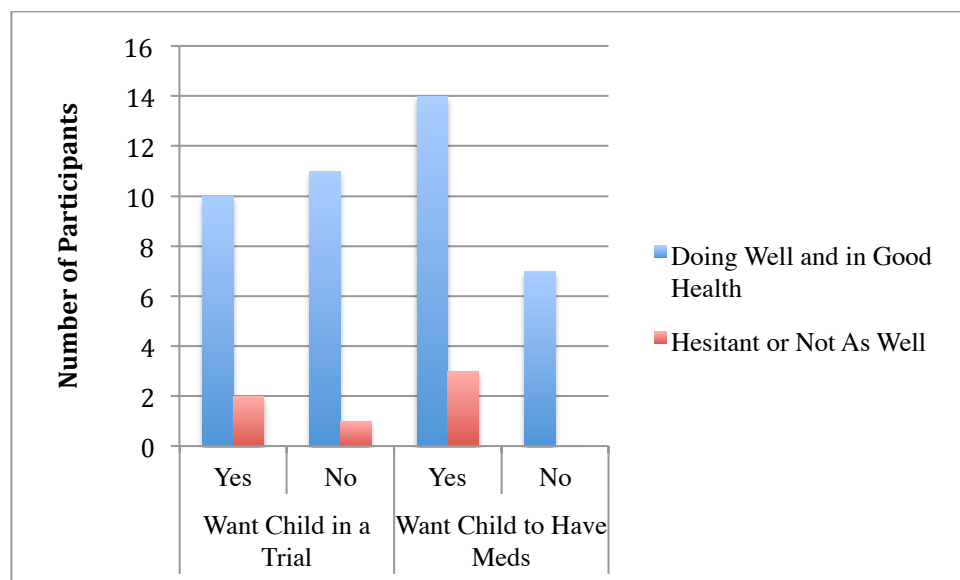
Of the 21 parents responding 'absolutely yes', 17 also explained that their child has problems with behavior and/or communication and four explained that their child has medical problems. One 'absolutely yes' parent described her son's medical problems: "So first came Down Syndrome, and then came the thyroid problem, and then came the Hashimoto's, and then came the Celiac, and then came the diabetes, so they just surround him," (D8) but to the next question, *and overall would you say that he's doing well and in good health?* she responded, "yes, yes he is." (D8) Of the three parents who did not say their child was doing well and in good health overall, one parent described her child as having behavioral, communication, and medical problems, one described his son as having behavioral and communication problems, and the other described her daughter as having communication problems, but no other problems since her Atrioventricular canal (AV) repair.

Although the sample was too small for statistical tests, we looked for correlations between a child's behavioral problems and the parent's interest in drug trial participation (Figure 8). Of the group of parents of children with behavioral problems, more parents did want their child in a trial than those who did not (45.5% vs. 18.2%); however, among parents who reported that their child had no behavioral problems, this same pattern was noted. That is, more parents were interested in having their child participate in a drug trial than those who were not interested in trial participation (53.8% vs. 38.5%).



**Figure 8: Effect of Child’s Behavioral Problems on Drug Trial Participation Interest**

We looked at the correlation between how parents perceived their children to be doing overall and their interest in enrolling their child in a trial or putting their child on medication. Of the parents who perceived their child to be doing well and in good health, the majority did not want their child to be in a trial (52.4%) (Figure 9). For the group of parents who were hesitant to say their child was doing well and in good health, more wanted their child in a trial than did not want their child in a trial (66.7%) (Figure 9). Notably, the difference was only one participant in both groups, so there was not as strong a correlation as was hypothesized. The group that did not perceive their children as doing as well did show expected results: all three parents in this group claimed that they want medication for their child.



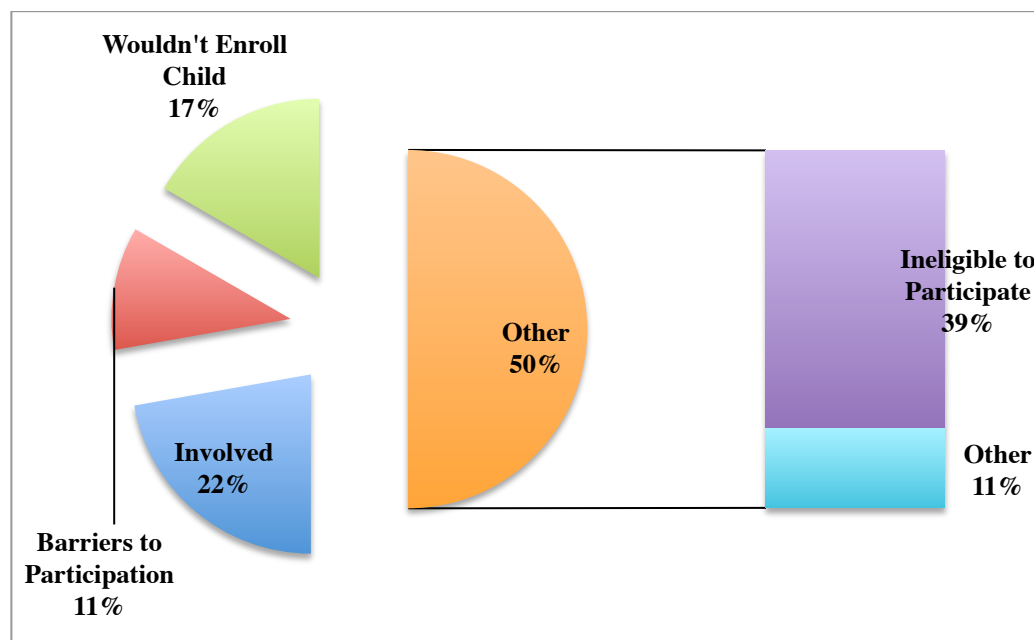
**Figure 9: Effect of Perception of Child’s Overall Health on Trial and Medication Interest**

### *Attitudes Towards Drug Trials*

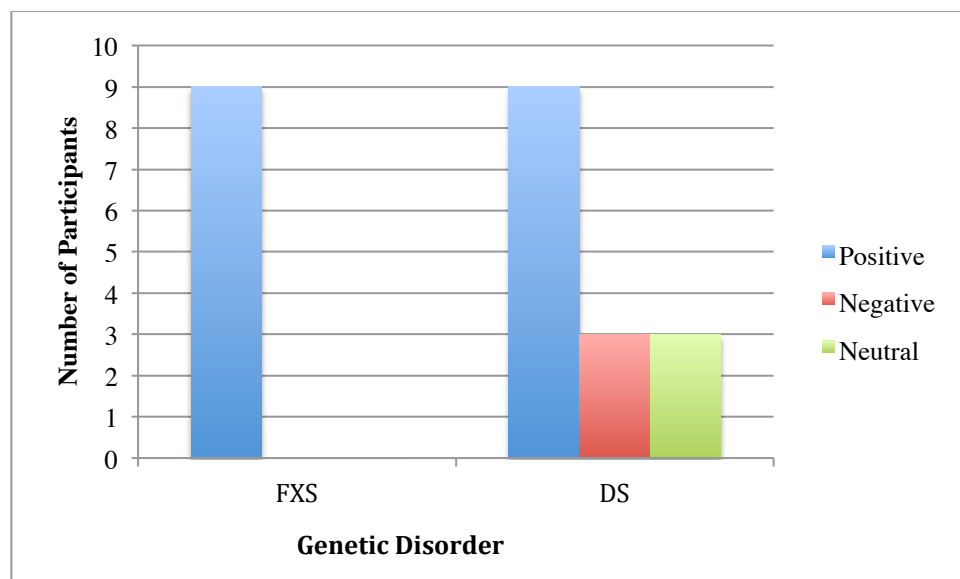
We asked parents about their attitudes on clinical drug trials and looked at the responses with respect to whether they had a child enrolled in a trial. Eighteen parents had positive feelings towards drug trials, specifically targeted therapies. One parent explained, “I think they are a miracle, it's an amazing time to live in and we’re honored to be a part of something, to be actually looking at Fragile X itself and not just the symptoms.” (F15) Three participants had negative feelings towards trials. When asked her feelings towards drug trials, one participant just responded “skeptical.” (D23) Three participants were neutral, in response to being asked their feelings towards drug trials; one of these parents explained, “I guess it would be a drug-by-drug basis.” (D9) Of the 18 who had positive feelings towards trials, five had already involved their child in a trial, five parents had children who were ineligible, three said they would never involve their child in a trial, and four wanted to involve their child but could not due to barriers to participation (Figure 10). One parent who spoke positively about trials but would not involve her child explained, “[drug trials] are necessary, I wouldn't volunteer my children for them.” (D20) “Barriers to participation” included logistics such as the family moving, the birth of a child, and hatred for blood

draws. Because trials for individuals with DS are only studying individuals between the ages of 18 and 30, many younger individuals with DS were unable to participate, and thus categorized as ineligible to participate in a trial (for the purposes of this study). Children unable to stop taking current medication in order to participate in a drug trial were also considered ineligible to participate. Two parents who have children in this situation also voiced concerns about the “double-blind” aspect of clinical drug trials. One parent explained,

I had planned, when clinical drug trials started, to be first in line with them. But ... they would have to come off of their medication before they could participate... I think [trials are] wonderful, wish we could participate, [I'm] very excited about them [but] it's the fact that they're double-blind, and it would be quite an undertaking to do this, and with the idea that they may not actually be getting the medication. (F24)



**Figure 10: Parents With Positive Feelings About Clinical Drug Trials**



**Figure 11: Attitudes Towards Drug Trials in General**

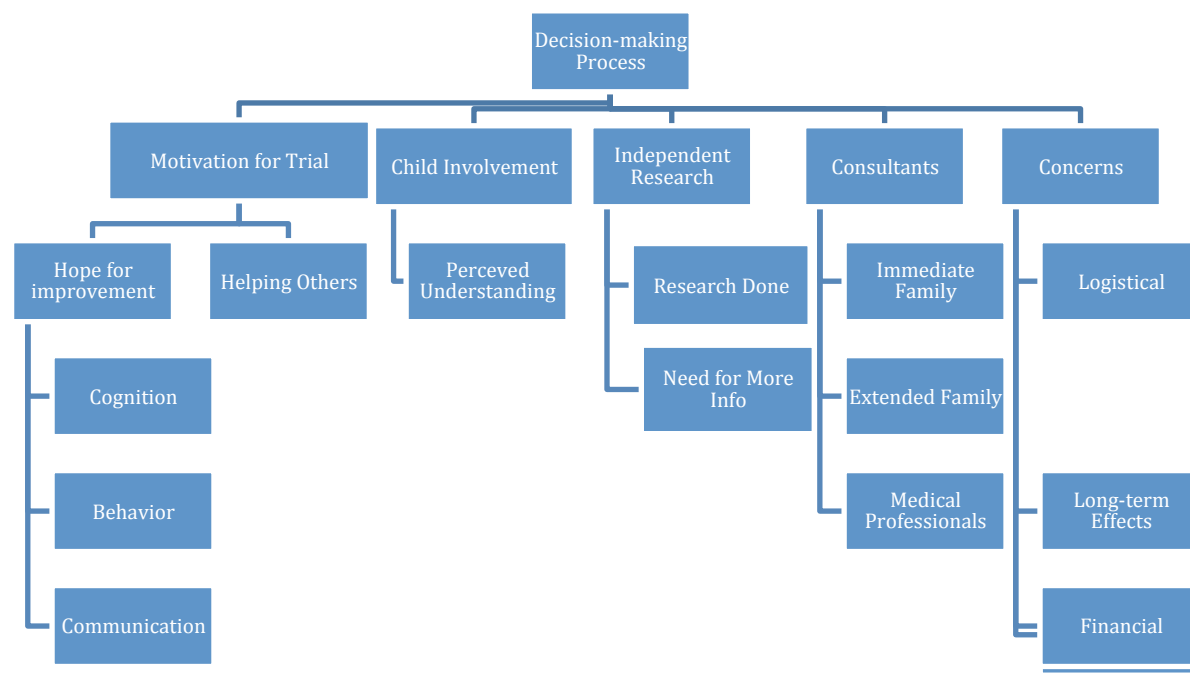
Attitudes towards drug trials were also broken down by genetic disorder (Figure 11). Of the nine parents of individuals with FXS who had positive feelings about drug trials, five parents have enrolled their child(ren) in a trial, two have children who are ineligible, and two have children facing barriers to participation. Of the nine parents of individuals with DS who have positive feelings towards drug trials, five have children who are ineligible, and three parents would not enroll their child in a drug trial.

Six children of the participants were currently, or had previously participated in a trial. The parents of all six children were glad their child was/is involved with a trial and described the perceived benefits since beginning the trial. One mother whose daughter was in a trial for FXS was asked whether any benefits were observed and she stated “I said before she was real shy, which she still is, but she's more open and forthcoming with answers, her memory has improved, her personal hygiene, daily routine has really changed a lot. She has a very positive attitude, which she may have had ... before but she demonstrates it more.” (F12) Other perceived benefits included communication improvements, including eye contact, interactions with peers, and improved behavior control.

## *Trial and Medication Decision-making Process*

### Motivation to be in a study

Many aspects of the decision-making process proved very important to parents discussing their attitudes towards drug trials and medication. Motivation for trial, child involvement, independent research, consultants, and concerns were significant through this process (Figure 12).

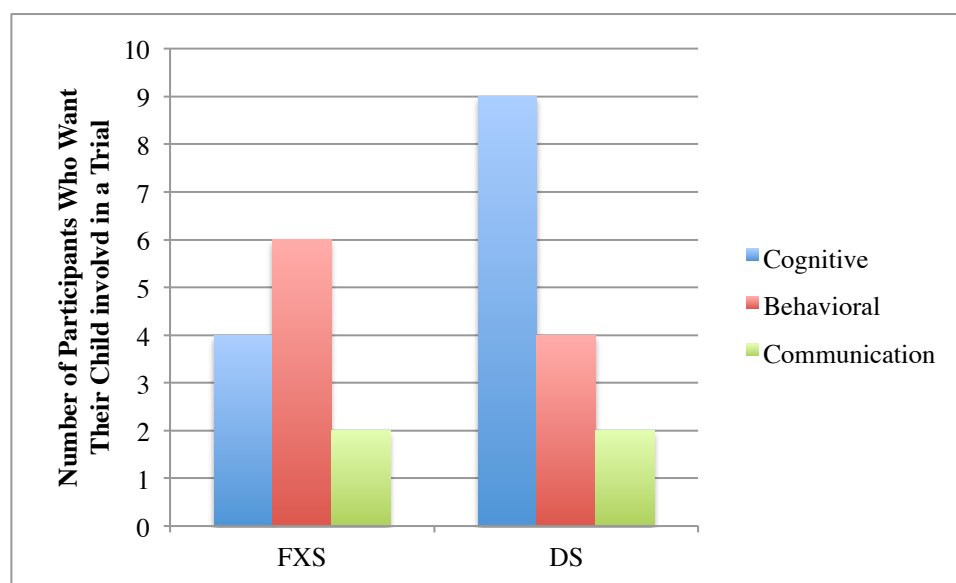


**Figure 12: Decision-Making Process for Clinical Drug Trials**

“Motivation for trial” indicates why a parent either decided to enroll his/her child in a clinical drug trial, or what would cause a parent to seek out or enroll his/her child in a trial. For example, in response to being asked “what would make you decide to enroll your daughter in a trial?”, one parent explained, “hoping that things would change and make a better life for her, her quality of life would improve.” (F12) “Hopes for improvement” refers to symptom alleviation, or benefits for which parents are hopeful in enrolling a child in a clinical drug trial or using an investigational medication. One parent responded to the same question: “to help his speech development, and social skills, improvement of his mental



capacity ... and also to hopefully help others as well,” (F15) explaining the specific areas where she would like to see improvement. Thirteen out of twenty-four parents were hopeful for improved cognition, 10 out of twenty-four wanted to see behavioral improvements, and four out of twenty-four were hopeful for improved communication skills. Figure 13 breaks these categories down by FXS and DS.

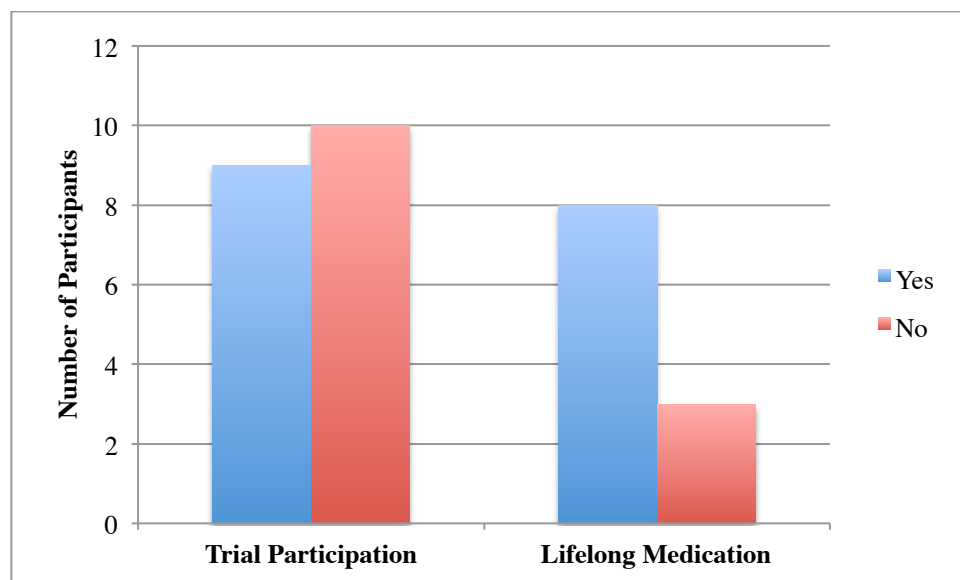


**Figure 13: Parents’ Hopes for Improvement from Trial Participation**

Five parents made comments indicating that part of the reason they wanted their child(ren) to participate in a drug trial is to help other individuals with the same genetic disorder.

#### Child Involvement

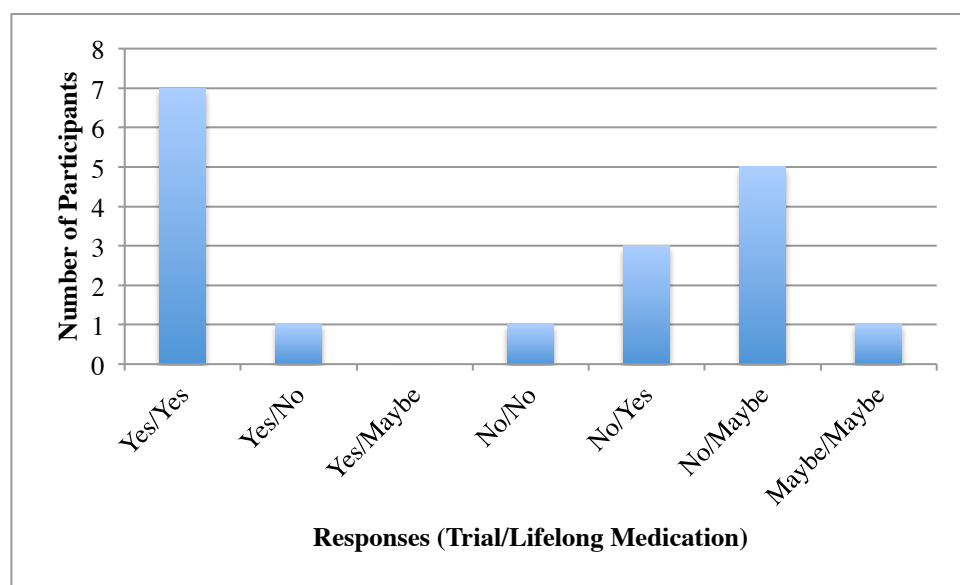
“Child involvement” was also found to be a very important aspect of the decision-making process. Nineteen participants were adamant about whether or not they would involve their child(ren), or had involved their child(ren) in a decision to enter a drug trial and 11 parents were adamant about whether or not they would involve their child in a decision for him/her to take a lifelong drug (Figure 14). The other parents explained that multiple factors that would determine potential child involvement, including cognitive function and understanding, and the child’s age.



**Figure 14: Child Participation in Decisions about Trial Participation and Lifelong Medication**

We also examined whether the parents' attitude towards involving their child in a decision to be in a trial was similar to that for lifelong medication (Figure 15). The response before the backslash refers to involvement about participating in a trial, for example a "no/yes" response means that parents would not involve their child in deciding to participate in a trial but would about taking lifelong medication (Figure 15). Of the parents who had enrolled their child(ren) in a clinical drug trial, two parents involved their child in that decision, whereas three parents did not. "Perceived understanding" was important in a parent's decision to involve his/her child in these decisions. For example, when asked about involving her daughter in her decision for her to participate in trial, the mother responded, "I doubt it, I doubt it. I doubt she'd understand" (D5) exemplifying the mother's perception of her daughter's understanding of potential participation in a drug trial. When one participant was asked if she would involve her daughter in deciding whether to take a lifelong drug she responded, "if she understands. It all depends on her level of understanding as for any of our children... no matter their chromosome count. But [whether we] try to explain that to her that this helps you talk better, understand more, or whether we would just explain it as just vitamins that everybody should take to keep them healthy... Just explain to her that this is just what

you do and this is part of it.” (D7) Another mother explained, when asked how much she involved her son in deciding about enrollment in a trial, “None, I’m sorry, he doesn’t have the mental capacity to decide.” (D16) Another parent responded “we discuss so many things with him that we would, you know, discuss all of this with him. He’s really fortunate to be able to comprehend a great deal.” (D21)



**Figure 15: Child Involvement in Decisions about Trials and Lifelong Medication Decisions**

One parent who would not involve her child in a decision to participate in a drug trial but would involve him in a decision to take a lifelong drug (“no/yes”, Figure 15) explained, “I would probably need to make [the decision for him to take a lifelong drug] when he is old enough to make the decision to I guess. It would depend on his input I guess, if he took it for his entire life.” Then, in response to being asked “so in terms of the clinical trial, would you want to include his input and wait until he is older or would you not necessarily?” she responded “Um, not necessarily but I mean if it’s an optional drug and it’s something that he would take after he was old enough to decide whether or not he wanted to take it then, if you talk about, for the rest of his life then he would control that.” (D4) Another response to the question about involving their child in a decision to participate in a drug trial was, “We would let him make the ultimate decision if he was older.” (D22) Other responses to the question of whether or not parents would involve

their child in the decision for the child to take a lifelong drug include: “the answer is yes, unless he's not at a point where he would comprehend a discussion like that, but that speaks for itself right, so the answers is yes,” (F18) “Yes. Also it would depend on you know, how much as we went along, how high functioning he already was. And the higher he was then probably the more say I would allow him to have in that,” (D19) and:

I think because of the cognitive delay, kids with Down Syndrome are going to be very easily swayed by people who may or may not have their best interest at heart, or they may have their best interest, but they're not working with a full set of knowledge, because something hasn't been tried for many years, so I'd be very careful about how I involved him. I would want his opinion, but I would also want him to really understand the decision. (D23)

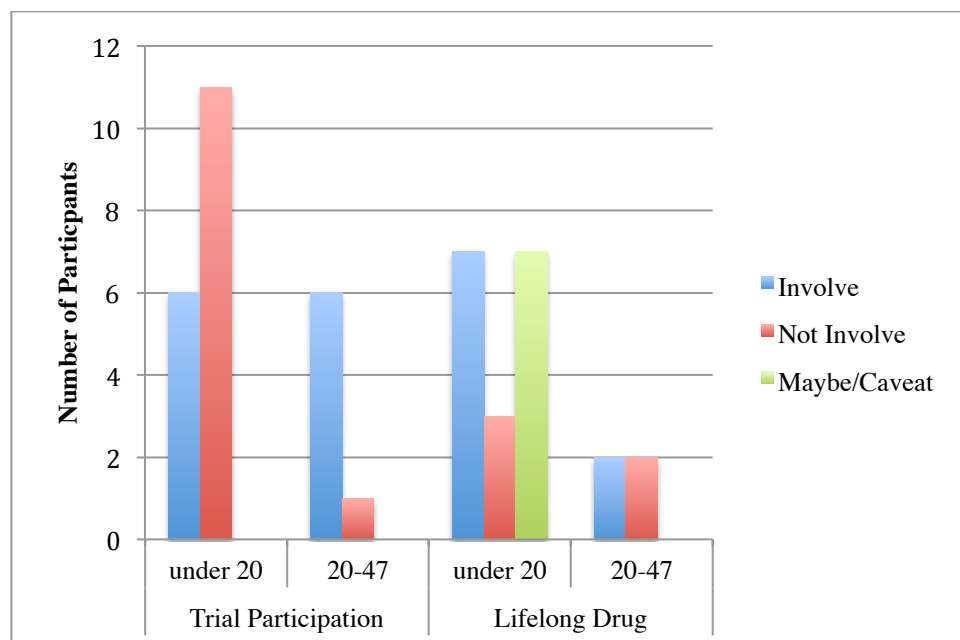
One parent of two children said “I would see if I could talk them into it. You don't really push them into doing something they don't want to do, so I would have to get their cooperation [to participate in a drug trial]” but later said, “No, I would not [involve them in a decision about taking a lifelong drug] they would not understand that.” (F24) Another parent said, “we would probably talk to him [about a drug trial] first and see if he was okay with that. I don't know if he'd fully understand but I probably would ask his permission first.” (D10) When asked what she would do if she wanted her to son to participate in a trial, but he said that he did not want to, another mother explained, “I would just talk to him talk to him see if I could try to explain it to him the best that I could, other than that if he refused, I couldn't really force him.” (F13) Before having her son enrolled in a trial, one mother considered “whether [her son] was willing to do it” later in the interview, she explained that her son “was the one who decided yes.” (F14)

Seven parents mentioned that as their child got older they would definitely involve him/her in a decision either to participate in a trial or take a lifelong medication. For example, when asked if she would put her daughter on lifetime drug, one parent of a four year-old explained, “depending on [her] age, I mean as she got older it would be up to her and she would be included in that.” (D9) Another mother was asked “if at all, how much would you involve your daughter in a decision to participate in a drug trial, “not at all, she is five years old with the mental capacity right now that matches our three-year-old. She wouldn't understand. Now, that might change as she grows and develops, but right now it's like any other decision

with regards to her healthcare, it's being made for her.” (D7) One mother, who has two children participating in a FXS trial did not involve her children in that decision but said she would involve them in a decision to take a lifelong drug:

Yes, yes, and I would say with my daughter now at age 9 almost 10 we do talk to her about when she tries a drug whether she likes it. Does she like it, does she feel like it's helping her, does she feel umm, for example we just changed her Adderall dose from 10 mg a day to 15, I asked her this morning does she like it better, does she feel like she understands it better, is it working better than the 10 mg, is she having any side effects, and I describe the potential side effects, and then she tells me whether she wants it, and like some of the drugs, like sometimes she takes trazodone to help her sleep and I'll ask her if she wants it, if she feels like she needs it that day, so yes.  
(F17)

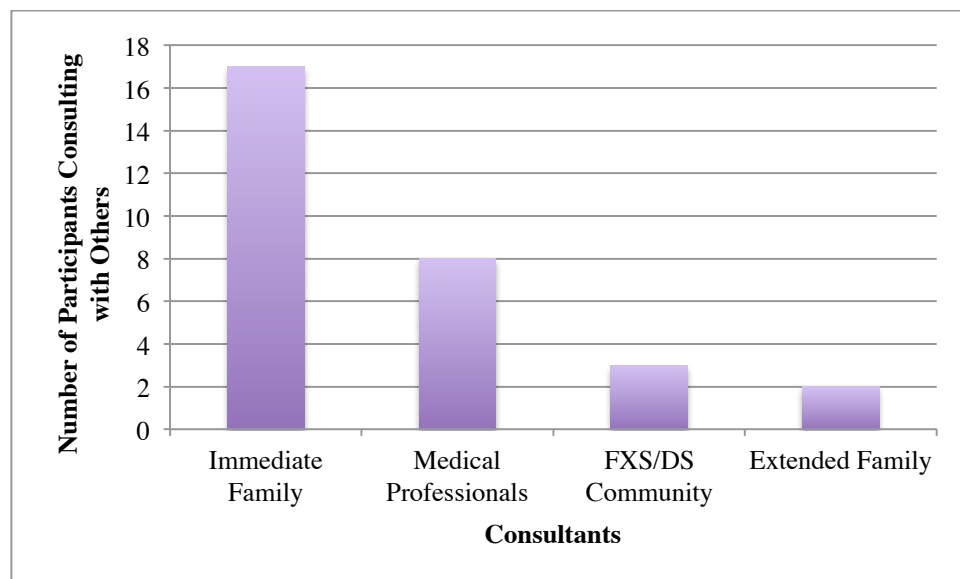
Because seven parents mentioned that they would involve their child in decisions when they got older, we looked at the effect of age group on child involvement in clinical drug trials and lifelong medication. For drug trial participation, 11 parents who have children under the age of 20 would not involve their child in the decision, whereas six would (Figure 16). In the group of parents who have children between the ages of 20-47, six would involve their child in that decision, whereas one would not. For lifelong medication, seven parents who have children under the age of 20 would involve their child in a decision to be on lifelong medication, three would not, and seven said maybe or yes, as the child got older. In the group of parents who have children between the ages of 20-47, two parents would involve their child in this decision, and two would not (Figure 16).



**Figure 16: Effect of Age on Child Involvement in Decisions about Trial Participation and Lifelong Drug Use**

Background knowledge about clinical trials varied among the parents who were interviewed. Some parents had independently researched clinical trials by speaking with physicians, speaking with other parents involved in clinical research, or researchers. One parent said “we have researched the possibility of [the trial] with our neurologist.” (F17) Six parents stated that they needed more information about clinical trials, “I just don’t know enough about [clinical trials]...so I would really have to be educated that this was really the right thing.” (D23) Twenty-three out of the 24 participants spoke or would speak with other people about their decision to enroll their child(ren) in a clinical drug trial. The most frequently mentioned consultants included immediate family members (spouse or children), medical professionals (researchers, physicians, and genetic counselors), FXS/DS parent community, and extended family (e.g., grandparents and uncles) (Figure 17). One parent explained, “my spouse would be right there with, me and [my daughter’s] brother who is sixteen, and her uncle actually who doesn’t live with us but lives in an

apartment behind our house and is a nurse administrator at Emory, so...in terms of some of the clinical kinds of questions that we might not be able to answer he would be a real resource in that regard.” (D6)



**Figure 17: Drug Trial Decision-Making Consultants**

Seventeen parents discussed concerns about enrolling their child in a trial or putting their child on medication. Fifteen out of the 24 parents interviewed expressed concerns about the safety of the drug, such as long-term and short-term side effects. One parent explained that she “worr[ies] about ... the long-term effects.” (D23) Four out of 24 parents mentioned logistical concerns, such as proximity to a clinical trial site and how the trial schedule would affect their everyday life. For example, one parent explained, “I’ve already mentioned that we’re real busy and if anybody offered something from January to March I’d say no way, I don’t have any time in my schedule for that, I’d look at my schedule and see what was logistically possible.” (D2)

Four parents also explained that there were personality traits about their child(ren) that they would not want to be affected by any medication. For example, “we [have] a child with Down Syndrome and they’re so happy and carefree and we wouldn’t want that to change.” (D19) Another parent compared targeted therapy to changing a trait or characteristic: “like if I have a headache I take an aspirin right? but

I'm -if I'm 5 foot four and there was a medicine that I could take to make me taller you know I'm not going to take that." (D23) Later the same participant said, "I don't feel like he's unhappy or broken or can't do anything, he's perfect... What I don't want is a pill that makes him, yeah know, comatose, all of a sudden, he's very easy for people to watch, but he's not learning anything if he's not himself anymore." (D23) In response to being asked her feelings towards drug trials, one other participant said, "I guess it would depend what it is, what they're purporting to do, and not against individuals being who they are cognitively, ... if it's something that has more of a global benefit than just targeting some kind of intelligence increase then I might be for it, but generally I just believe, let people be who God created them to be." (D5) On the opposite side of the spectrum, one parent explained that she would give her daughter anything: "the retardation, IQ factor, gosh if there was something out there that would guarantee her IQ to raise her understanding, absolutely I'd look into it. ... We do know that she will succeed, but if I can give her more heck ya, I would, I'd do with my normal kids too." (D9)

### ***Attitudes Towards Medication***

Throughout the interviews, three out of twenty-four participants stated they had negative feelings towards medication. For example, one parent explained, "if we can manage behaviors with other things besides medicine, that's the way I tend to go," (D20) implying that she tries to shy away from medicine when possible.

Parents were asked their feelings towards potential medication targeting FXS and/or DS on the market that had been proven to be safe and effective, and the use of such medication for an individual's lifetime. Participants were asked "if a drug came on the market would you consider getting a prescription for your child?" All 24 of the parents said 'yes', however 10 of those said that their 'yes' would be contingent upon certain caveats, such as health insurance coverage, needing more information, knowing which symptoms the drug would target, wanting more information, knowing that the drug is safe, depending on what symptoms it purports to affect, and how long it must be taken to see results. Parents



were also asked whether they would put their child(ren) on a drug for an entire lifetime: 12 said ‘absolutely yes’ and two said ‘no’. The remaining 10 were undecided and had caveats. Reasons for their hesitancy included: long-term effects, including side effects, the child’s input (as the drug would be taken for the entirety of his/her life), and the child’s age.

### ***Misconceptions/Misunderstandings about Trials***

Of the 19 participants who do not have a child currently enrolled in a trial or who have previously been enrolled in a trial, six brought up needing more information before making a decision about trial involvement. Six participants, only one of whom also mentioned that she would like more information, said they had little to no general knowledge about clinical drug trials. Thus, 11 out of the total 19 participants who do not have a child or children participating in a clinical drug trial indicated that they did not feel fully educated about clinical drug trials. Comments throughout interviews also indicated participant misunderstanding about clinical drug trials. One participant, when asked if she knew about clinical drug trials in general, explained, “not really, this is the first one.” (D8) Another participant, when asked about the decision-making process if she did decide to enroll her child in a trial, explained “I guess the only way that we would participate in a trial is... obviously FDA approval.” (D22) A few other parents made comments about only wanting their children to participate in a clinical drug trial if there were no side effects and no possible harm to their child.

### **Discussion**

The purpose of this study was to explore the factors influencing parental decision-making about drug trial participation and treatment for individuals with FXS or DS. This sample in no way fully represents the community of parents who have children with FXS or DS; this study was simply to begin exploring this topic and gauge common factors affecting parental decision-making. To achieve this, recurring themes were analyzed to understand the decision-making process of the participants involved in this study. The principal factors influencing parental decisions in this population were found to be: health

of the child, how much parents could and would involve their children in a decision to participate in a clinical drug trial or take lifelong medication, attitudes towards trials, attitudes towards medication, and misconceptions/misunderstanding about trials.

### ***Health of the Child***

For this study, the most important aspect of the health of the child is the parent's perception of the child's overall health and well-being, a theme leading to interesting and surprising results. Before conducting interviews, we expected parents would describe their child as doing well overall only if their child did not have communication, behavioral, and medical problems. Twenty-one parents quickly responded that their child was in good health, and only three individuals responded differently or questioned the term 'good health', irrespective of whether they had just described communication, behavioral, and/or medical problems. These three individuals implied that intellectual development plays a role in their perception of well-being. These data pose the question, *what does it mean it to be in good health and doing well?* A study by Kaplan et al agree that there is no one way to define health and well-being.<sup>32</sup> Similarly, Larson's work describes four different definitions of health.<sup>33</sup> Felce also differentiates between different types of well-being: physical and social.<sup>34</sup> Such literature illustrates different definitions and perspectives when it comes to explaining *health* and *well-being*. Thus, in our study, it was difficult to predict how participants would answer the question *does overall health depend on communication, behavior, medical problems?* Our findings showed that the majority of participants describing their children as having such problems very quickly affirmed that their children were absolutely doing well and in good health. Participant 9 even posed the question of how to define health, during the interview, implying that the term 'health' is relative.

Further, we hypothesized that parents with children who had more behavioral problems would be more likely to want to involve them in a clinical drug trial and those of children with less behavioral problems. However, on this point there was not a clear trend (Figure 8). More parents who perceived their

children to have behavioral problems did want to enroll their child in a drug trial than those who did not, but the difference was very small (Figure 8). However, more parents perceiving their children not to have behavioral problems wanted to enroll their child in a clinical drug trial than those who did not want to enroll their child in a trial (Figure 8). These results suggest that the child's behavior is not the sole factor influencing parental attitudes and interest in clinical trials. It could also be the case that parents whose children have more behavioral problems might worry that such behavior could interfere with the clinical trial procedures, and thus the parents might not be as interested in having their child(ren) participate.

Similarly, we expected parents who perceived their children to be doing well would be less inclined to involve them in a clinical drug trial and less inclined to want them to have medication. Again, findings did not strongly support this idea (Figure 9). One aspect of the new drugs targeting FXS and DS have focused on improving behavioral problems.<sup>10,22</sup> Because such medication is addressing behavior, we predicted that parents who perceived their children as doing well overwhelmingly would not want their child on medication. However, the opposite proved true: more parents who perceived their children as doing well and in good health wanted their children on medication than those in the same group who did not (Figure 9). One possible reason for this is that parents might be reluctant to describe their children as not doing well. Even the three parents who did not explain that their children were doing well overall did not say their children were unhealthy or doing poorly, they just questioned the term 'health' or qualified their response. Some literature addresses this issue in the context of treatment and the discussion of when to medicate. Parens addresses this discussion, and suggests two different definitions of 'health'; one definition describes "health as freedom from disease and [another defines it] as a state of complete physical, mental, and social well-being."<sup>35(p.3)</sup> Based on an individual's own definition of 'health' he/she might have a certain preference for or against taking medication. It is also possible that a parent might base his/her perception of his/her child's overall health on one definition, while considering a different definition in deciding whether or not to medicate the child. Parens cites an example of two males who are

the same age and height, one who has a growth hormone deficiency, and the other who does not.<sup>35</sup> He poses the question of whether or not both individuals should be treated with growth hormone; acknowledging that giving the child with the deficiency GH would be treatment, while giving the child with normal levels of GH supplemental hormone would be the enhancement of a trait.<sup>35</sup> Similarly, parents might think and perceive their children to be doing well, however still want to give them the greatest opportunity to ‘succeed’ and thus believe that medication can improve or enhance their functioning. Given the GH example, the parent of the child without the GH deficiency might describe the child as doing well and being healthy, but still hope and want some type of medication for the child. Parents’ discussion of treatment versus enhancements helps shed light on our findings. From these data, it seems that overall health perception contributes to a parent’s decision to enroll their child in a clinical drug and take medication.

### *Attitudes Towards Drug Trials*

Some individuals are predisposed to have negative feelings towards drug trials, for a variety of reasons. We wanted to see how many participants felt negatively about trials to assess how much this influenced parents’ decisions about enrolling their child in a drug trial. The fact that only three of the 24 participants felt negatively about drug trials demonstrates an overall positive feeling. This could be biased because the majority of our participants were recruited from Emory University and had already participated in research. People participating in research might be more likely to think positively of clinical research. People who think negatively of clinical research may also be less likely to have participated in this study. Another qualitative study assessing attitudes towards medical research similarly asserted that such a study might select for individuals who have positive feelings towards research, providing somewhat biased results.<sup>36</sup> Further, of the 18 participants who felt positively about drug trials, three parents explained that they would not involve their own children in a trial (Figure 10). Thus, attitudes towards drug trials alone did not determine a parent’s decision or interest in involving their child

in a clinical drug trial. Note that none of the parents who had neutral or negative attitudes towards drug trials have enrolled their child in a drug trial. However, this could also be the case because DS trials are not currently involving children.

Notably, the ‘double-blind’ aspect of drug trials was mentioned as a concern by three parents. Two of those parents had children who could not stop their medication to participate in a trial and one parent whose son did participate in a trial but was given the placebo. Unfortunately, clinical drug trials must be carried out in this way to preserve the integrity of the study and accurately gauge the safety and efficacy of new drugs. Irrespective, it is a point of concern for some parents in considering clinical drug trials. Other studies have also surveyed attitudes towards the ethics of clinical drug trials. Cassileth et al found that 62% of their study participants believe clinical drug trials in the United States to be ethical, while 31% are not sure how they feel, and only 6% believe such trials in the U.S not to be ethical.<sup>37</sup> Notably, the questionnaire for their study did not ask about the double-blindness of studies or use of a placebo. Another study, examining a population of patients with Schizophrenia, directly asked participants if they “would...be willing to participate in a placebo-controlled clinical trial.”<sup>38 (p.278)</sup> Results indicated that 56% of participants said no; after responding ‘yes’ or ‘no’, participants could then indicate why they felt the way they did.<sup>38</sup> Two reasons under the ‘no’ category were similar to parents’ explanations in our studies.<sup>38</sup> As mentioned, parents in our study worried that their child would stop current medication, receive a placebo in a trial, and thus be giving up current treatment, and second, that they would want to know their child was receiving medication. Similarly, Hummer et al devised a questionnaire that offered the following reasons for not wanting to participate in a placebo-controlled study: “not receiving medication might worsen my condition or slow improvement [and] I want to know whether I am really receiving medication.”<sup>38 (p.278)</sup> While this group of participants is very different than the group in our study, similar findings portray the same concern with placebos and double blind studies that were found through our project.

Our findings indicate that there may be a difference in parental attitudes about clinical trial by FXS and DS status, where parents of children with FXS are more positive about trials (Figure 11). One explanation is that FXS trials have been going on longer than DS trials, and include a wider range of ages. This allows more parents to have knowledge about trials and also see benefits of past trials. Surveying more parents of individuals with FXS and DS would be important to determine other reasons for this potential difference.

It is important to note that all of the parents who have had their child involved in a trial were very glad for their child's participation and explained improvements in the child's behavior and speech, since beginning the trial. Even the mother whose son was given a placebo was glad that he participated and that they were able to participate in research and contribute to science. Mattson et al surveyed participants in two clinical drug trials (the Beta-Blocker Heart Attack Trial (BHAT)) and the Aspirin Myocardial Infarction Study (AMIS)) to gauge whether the participants felt they had benefited from the study.<sup>39</sup> Eighty-four percent of AMIS participants expressed benefits from AMIS, while 27% expressed negative feelings after participating.<sup>39</sup> The overall positive attitudes after drug trial participation in the study by Mattson et al corroborate our findings that parents whose children were involved in clinical drugs trials were positive about them and felt they had benefitted from the trial.

### ***Trial and Medication Decision-making Process***

As expected, the decision-making process for clinical drug trial involvement proved to encompass many important factors that influence parental decisions regarding their children's clinical drug trial participation and medication usage. Overwhelming, the DS interviews were hopeful for cognitive improvement, whereas the FXS interviews were hopeful for behavioral improvements. Figure 7 illustrates parents of individuals with FXS reported more behavioral problems than did parents of children with DS. The fact that five parents cited 'helping others' as motivation to participate in a trial speaks to the strength of the FXS and DS communities, and their unity.

One of the most important aspects of the decision-making process is child involvement, a recurring theme in every interview. The fact that most parents had differing opinions about whether they would involve their child in a decision about participating in a drug trial versus taking medication, implies that different factors influence each of those decisions (Figure 13). However, the fact that the topic of child involvement did come up in every single interview indicates that parents have a clear hope of involving their children in decisions about experimentation and treatment as they get older and are able to understand their diagnosis and drug trials. This demonstrates that ethics are at the forefront of this topic, and parents are thinking about when and how they can involve their children in decisions about their own health and treatment.

On the whole, parents were more likely to involve their child in a decision to take a drug for his/her entire lifetime than to participate in a drug trial (Figure 14). It makes sense that more parents would involve their child in a decision to take a lifelong drug, because as the child ages the individual might become responsible for taking his/her own medication. Parents of younger children tended to say that as the child got older they would involve him/her in such decisions, however parents of older individuals (20-47) did not unanimously involve their children in these decisions. Notably, parents agreed that they *thought* they would involve their children in these discussions with age and development, however this was not necessarily the case among the parents of older individuals (Figure 16). As evidenced in responses, some parents would not move forward with a trial without a child's consent, whereas other parents said they might tell their child that their medicine was vitamins that everyone takes. Age of child played a role in child involvement in decisions about clinical drug trial participation, as most parents of older children would involve their children in a decision to participate in a drug trial, whereas most parents of younger children would not or did not involve their child in that decision (Figure 16).

Twenty-three out of the 24 participants would consult other people when making a decision to enroll a child in a clinical drug trial, indicating that the participants wanted other opinions or support

before making such a decision. Most of the time, support was sought from their child's immediate family members.

The child's safety was one of the recurring concerns in parental decision-making to enroll a child in a clinical drug trial. Even medications that have been FDA approved and on the market for years have safety problems. Every individual is different and can have different responses to medication. Some of these safety concerns can be alleviated, as the drug trial moves into the next phase of efficacy; however safety concerns will never go away completely, as some individuals will continue to worry about possible side effects and long-term effects despite available research. Safety concerns about medication will continue to deter some parents from looking into clinical drug trials.

Another concern that was less prevalent than safety of the drug was the notion of how a drug might change a participant's child. One next step is to interview parents of children who do not have FXS or DS, but take medication for behavioral problems such as hyperactivity, social withdrawal, and anxiety to explore whether these concerns are limited to this population of individuals with FXS and DS, or if they are shared among parents of children on behavioral medication as well.

### ***Attitudes Towards Medication***

Parental concerns about changing their child relate to attitudes towards medication and the treatment/enhancement distinction.<sup>35,40</sup> Levy explains, "there is an "important...distinction between the *treatment* of disease, and the *enhancement* of traits."<sup>40(p.73)</sup> Parens discusses this idea of health and the purpose of medicine, explaining the work of Norman Daniels, who says,

disease and disability are seen as departures from species-typical normal functional organization or functioning...according to the normal function model, the central purpose of health care is to maintain, restore, or compensate for the restricted opportunity and loss of function caused by disease and disability. Successful healthcare restores people to the range of opportunities they would have had without the pathological condition or prevents further deterioration.<sup>35 (p.3)</sup>

In other words, this explanation of health and medicine suggests that medicine should be used to restore



an individual to a level of functioning that would be possible without the current condition affecting the individual. Because targeted drug trials for intellectual disability are so new and aim to target the biochemical effects of FXS and DS, they are in many ways using a medication to restore functioning that would be possible without the condition. In the past, behavioral drugs have been used in an attempt to treat some problems typically seen with FXS and DS, such as the anxiety, hyperactivity, impulsivity. But arguably, targeted trials attempt ‘to restore people “to the range of capabilities they *could be expected to have had* without...disability.’”<sup>35(p.6)</sup> Parens further distinguishes between treating diseases and enhancing traits, explaining that “the purpose of medicine is not to eliminate all differences.”<sup>35(p.6)</sup> Participants in our study even alluded to this distinction by comparing treating a headache to enhancing growth, and expressing a concern that medicine and trials might change children. In the future, it would be important to consider whether there is similar parental concern about treating individuals with behavioral problems who do not have an underlying condition. For the purpose of this project, it is important to understand this very real, recurring concern throughout interviews as a factor that influences parental decision-making in considering clinical drug trials.

Clearly, parental attitudes towards medication in general play a role in their perception of clinical drug trials and their willingness to enroll their own child in a trial and their interest in trials and medication for their child. To some extent, preconceived notions about medication in general surely factor into parental decision-making about clinical drug trials and lifelong medication.

The recurring notion that parents tend to prefer medicine treating a *medical condition* versus a *trait* conveys a different perception of their child’s disorder-related conditions, while relates to Levy’s discussion.<sup>40</sup> New targeted therapies for FXS and DS are attempting to target biochemical changes resulting from an FMR1 mutation, or the presence of a third chromosome, which are medical conditions. Thus, such therapies attempting to reverse the biochemical consequences of the inherited conditions are more like the treatment of a medical condition, than changing an individual’s traits. Because these therapies target cognition and behavior, two critical components to a person’s character, this issue is very

complex. Further, there is clearly a concern amongst parents that such medication can result in the change of an individual's trait.

### ***Misconceptions/Misunderstanding of Trials***

Through this project, interviews illustrated much about participants' understanding and knowledge of clinical drug trials. One recurring theme throughout interviews was parents' desire for more information, indicating an overall lack of education about clinical drug trials. Comis et al study surveying cancer patients' attitudes towards clinical drug trials likewise found "more than eight out of ten [cancer patients surveyed] don't even consider the possibility of participating in a clinical trial for the treatment of their cancer because they are unaware that participation might be an option."<sup>41(p.3)</sup> Again, this study relied on a different population than ours did, however similar results demonstrate a universal lack of knowledge regarding clinical drug trials.

Parents' comments quoted in the results section illustrate that some participants did not understand that trials testing the safety of new drugs occur before FDA approval. To be clear, some trials occur after FDA approval in the case that a drug is being tested for its efficacy to treat a condition different than its original indication.<sup>42</sup> One participant thought our phone interview was a clinical drug trial. A few parents also said they would not want their children involved in a trial unless there were no side effects or harm possible. Understanding clinical drug trials plays a role in parental decision-making to enroll a child in a trial. Before making a decision about whether to even *consider* participating or enrolling a child in a drug trial, let alone form attitudes towards them, individuals should have all of the information and understand the goals of each trial.

Such responses also suggest that trials with the goal of determining drug safety were not well understood. Prior to participating in a clinical drug trial, or any type of research, an *informed consent* form must be signed by potential participants. This form is important for explaining the research, any compensation for the participant, and any risks and benefits associated with the study.<sup>25</sup> While this form is

important for clarifying clinical drug trials for participants, the general public may make a decision not to participate in a trial before getting to the point of reading an *informed consent*, and thus may be deterred to participate in a trial based on misconceptions.

Lastly, the purpose of clinical drug trials is to test the safety of new drugs.<sup>43</sup> We found that parents wanting to involve their child in a clinical drug trial wanted to do so in order to improve their child's health or condition, and to help others. There may be some therapeutic misconception here as to the purpose of clinical drug trials, as parents interviewed did not mention testing drug safety as a reason for participating.

### ***Study Limitations***

#### ***Recruitment***

Recruitment was primarily done at Emory University and included individuals who are either involved in ongoing clinical trials at Emory University, or who see physicians at the Emory genetics clinic. Because of this, most of the participants have had some involvement in either clinical trials or other forms of research. To counteract any bias, recruitment flyers were also sent via email to individuals in the Georgia LINKS group, which is sponsored by the National Fragile X Foundation, to recruit individuals not participating in trials or previously involved in research at Emory. The majority of participants live in the Atlanta area; a few were from other states, however, conducting interviews on a more national level would provide a broader subject pool. Currently, DS trials only involve individuals between the ages of 18-30, already decreasing the eligible pool of individuals with DS as compared to FXS. Because the majority of the participants in the DS group have a child who is under the age of 18, none of the participants with a child with DS are currently or have previously participated in a trial. In the future, it would be beneficial to include parents of individuals who have a child enrolled in a clinical drug trial for DS in a similar study.

### Language

During interviews, it was important to use neutral language regarding clinical drug trials. We wanted to know parental attitudes and opinions towards trials and medication without promoting or dissuading participation. There was definitely a challenge in phrasing questions a certain way to get the most information from participants without implying that parents should hold a certain opinion about trials or medication. A social stigma exists against individuals with intellectual disabilities, and it is important to be careful with language when discussing intellectual development and genetic conditions.<sup>44</sup> One participant made a comment that she found one question to be off-putting: In response to being asked, “what symptoms do you consider to be the most important to be controlled by a drug?” she explained, “I guess I find that question a little, I’m a little put off by the question... I don’t know that there are any other symptoms per se that I would want to control.” (D20) She later suggested different wording of that specific question. While we tried to be very careful with wording and had many people who do research on FXS and DS look over the interview guide, one participant was uncomfortable with the language used, representing the importance of language in the discussion of intellectual disabilities. The Special Olympics has even published a guide, entitled *Ten Commandments of Communicating about people with intellectual disabilities* to encourage the use of certain language when discussing intellectual disabilities.<sup>45</sup> This guide coupled with While’s article illustrate the importance of using certain language in this discussion.<sup>44,45</sup>

### **Concluding Remarks**

The aim of our study was to look at the factors influencing parental decision-making about drug trials for children with intellectual disabilities. We have highlighted seven factors that influenced the decision of the twenty-four participants in this study: behavioral problems, parental attitudes towards drug trials, parental attitudes towards medication, hopes for improvement of child’s condition, parental concerns about the effects of clinical drug trials and medication, child involvement in decision-making,

misunderstandings about the nature of drug trials. Why do these factors matter in the context of decision-making for individuals who have intellectual disabilities? As mentioned before, intellectual disability can impair cognition and the ability to make decisions, an integral aspect of health care. Jones and Holden assert that “if [a] patient lacks decision-making capacity...a surrogate decision-maker must be consulted.”<sup>46 (p.975)</sup> Thus, in the case of intellectual disability, it is certainly possible that a surrogate or proxy will need to make decisions on an individual’s behalf. For this reason, it is important to understand decision-making and how it relates to the principles of bioethics: respect for persons, beneficence, non-maleficence, and justice.<sup>47</sup> The first of these principles, respect for persons, sometimes referred to as autonomy, values human beings as self-determining individuals who “enter into the research voluntarily and with adequate information.”<sup>48 (B1)</sup> Similarly is the concept of informed consent, which requires “information, comprehension and voluntariness.”<sup>48 (C1)</sup> Without the ‘comprehension’ aspect, informed consent is not possible, and thus individuals lacking decision-making capacity must rely on surrogates to consent to research participation. Beneficence and non-maleficence require people to do good and avoid harm, respectively. This is relevant to the case of clinical drug trials with individuals who are intellectually disabled because it is important for these decision-makers to be beneficent, and make decisions that weigh risks and benefits. In our study, many parents explained that they looked at potential harms and benefits to their children when deciding whether or not to enroll him/her in a clinical drug trial. With respect to clinical drug trials for intellectual disabilities, the principle of justice is important because it affords that individuals who are unable to make decisions for themselves will have surrogates who can make ethical decisions for them.

The seven factors that we found to contribute to the decision-making process about clinical drug trials and medication for individuals with intellectual disabilities are related to these principles of bioethics. Parental hopes for improvement of the child’s condition, child’s behavioral problems, and concerns about the effects of clinical drug trials and medication fit under beneficence and weighing the benefits of a trial. Child involvement falls under autonomy or respect for persons by respecting and

involving children in these decisions. Finally, parental attitudes towards drug trials and medication falls under justice, and the ability of parents to step in and make the best decisions for children who may have impaired cognitive capability. Misunderstandings about the nature of drug trials indicates the continued need for informed consent and making sure that research subjects are fully informed before agreeing to participate in any type of study.

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