Original Article

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Participation of underrepresented minority children in clinical trials for Fragile X syndrome and other neurodevelopmental disorders

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Summary **The purpose of this study was to identify demographic data, motivational factors and barriers for participation in clinical trials (CTs) at the University of California Davis, MIND Institute. We conducted a cross-sectional survey in 100 participants (81 females and 19 males). The participants had high education levels (only 2% had not completed high school), a mean age of 44 years (SD ± 9.899) and had at least one child with a neurodevelopmental disorder. The diagnosis of Fragile X syndrome (FXS) had a significant association with past participation in CTs ($p < 0.001$). A statistical significance for age of diagnosis and participation in CTs was also found ($z = –2.01$, $p = 0.045$). The motivating factors were to help find cures/treatments for neurodevelopmental disorders and to relieve symptoms related to child's diagnosis. Factors explaining lack of participation, unwillingness to participate or unsure of participation were: lack of information/knowledge about the trials, time commitment to participation (screening, appointments, assessments, laboratory tests, *etc*.) and low annual household income. These results show that a portion of underrepresented minorities (URM) not participating in CTs are willing to participate and suggests that reducing barriers, particularly lack of knowledge/ information and time commitment to trials are needed to improve recruitment.**

Keywords: Fragile X syndrome, autism, ASD, clinical trials, health disparities, URM, under represent minorities

1. Introduction

More than two decades have passed since the Congress (Revitalization Act of 1993) required that clinical trials, funded by the US National Institutes of Health, include members of underrepresent minorities (URM)(*1*). However, data from the US Census Bureau, National Institute of Health and Tufts Center for the Study of Drug Development (CSDD) demonstrate a clear disparity that exists amongst minority populations in clinical research (US Census Bureau, NIH, and Tufts CSDD, 2010) (*2*). Randomized controlled trials (RCTs) are considered to be the gold standard in evaluating medical interventions. The ability to trust and apply the results of clinical trials, as well as to transfer therapeutic treatments into clinical practice, is related to the type and number of patients enrolled in the studies (National Institute of Cancer, 2002) (*3*). With low minority participation in clinical trials, there is a lost opportunity to discover the effects of a drug-agent amongst URM and increases the existing health disparities within minorities.

Barriers to recruitment, participation, and retention in clinical trials for URM are complex, but can be grouped into 3 categories: *i*) the effect of the disease studied; *ii*) systems factors (*e.g.*, access to clinics, length of appointments or procedures, gap between seeking and receiving care and language barriers (most pharmaceutical companies do not translate the outcome measures into other languages); and *iii*) patient factors (*e.g.*, problems with medication, mental illness, incomplete understanding, race, economical status and mistrust of health care professionals) (*4,5*). Clinical trials in children are often underappreciated even when results have shown major improvements in health care. An illustrious example is the 5-year survival improved from 25% to more than 70% as a result of multicenter trials for acute lymphoblastic leukemia (*6*). However, when compared with adult clinical trials, the number of pediatric clinical trials remains low (*7*) and most of

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them are related to cancer.

The Health Resources and Services Administration (HRSA) and the Center for Diseases Control and Prevention (CDC) found that the prevalence of parent-reported developmental disorders (DDs) in children increased by 17.1% from 1997 to 2008 (*8*). With this rise, a push towards potential targeted treatments for neurodevelopmental disorders has led to multiple Phase II clinical trials for children with neurodevelopmental disorders including Fragile X syndrome (FXS) (*9*) and autism (*10*). Although several studies have proffered reasons for the relative absence of URM among clinical trial participants (*11-13*) to our knowledge none have specifically looked at participation of children with neurodevelopmental disorders. Here we present a small cross-sectional survey of factors associated with participation in clinical trials for children with FXS syndrome and other neurodevelopmental disorders. The intent of this study was to gather general demographic information and attitudes towards CTs amongst the parents of children with neurodevelopmental disorders. We also investigated whether or not URM groups are less likely to participate in CTs than their White counterparts, and whether URM groups were willing to participate in such studies in the future. Factors that impact the decision to participate in CTs were also gathered in order to identify barriers.

2. Methods

2.1. *Participants and procedures*

This study was approved by the Investigational Review Board of the University of California Davis and Touro University California. The research was conducted at the University of California Davis, Medical Center, MIND Institute in Sacramento, California, where about 22 clinical trials were conducted at time of the study. The cross-sectional survey was administered to parents who came to the MIND for their child's treatment and/or to participate in research.

The survey had twenty-nine questions, most of them with a multiple-choice answer and an additional space for free response. Demographic information was collected including: age, sex, race, ethnicity, educational level (if applicable spouse/partner data was also obtained), diagnosis and age of diagnosis, language spoken at home and annual household income. This survey looked at the attitudes of current clinical trials participants based on a four-point Likert scale ranging from "not at all important" to "very important". The questions were validated by a research committee that included multiple members of the MIND staff (physicians, psychologists, social workers, research assistants and volunteers) and patients. US Census's definition of minority was used in classifying the participants into URM and non-URM (*14*). Mean household income was classified according to the US Census (*15*).

2.2. *Data management and analysis*

The data was collected and managed using the REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the UC Davis CTSC. REDCap is a secure, web-based application designed to support data capture for research studies (*16*). The data was analyzed using Statistical Package for the Social Sciences (SPSS) for Windows, Version 21. Descriptive statistics and bivariate statistics included a Chi-square test for independence. Representativeness of sample respondents was assessed using Pearson's or Fisher's exact-test. Nonparametric statistical tests (Kruskall-Wallis tests, Wilcoxon rank-sum/Mann-Whitney U tests) with a significance level of 0.05 were performed for continuous and ordinal variables that were indicated as being a normal based on Shapiro-Wilk Normality test. An α level of 0.05 was used for all statistical tests and all *p*-values were given as two-tailed. A logistic regression analysis was performed for the outcome variable was 'participation in a research trial(s)' (yes/no) and 'future participation in clinical trial(s)' (yes, no, or don't know/unsure).

3. Results

3.1. *Responders demographic*

A total of 100 individuals participated in this survey. All respondents were asked to report their race in addition to ethnicity; 69 were White, 5 Black, 4 Asian, 1 North American Indian/Alaska Native, 18 "Other" and 3 did not respond. When all participants (n = 100) were asked for ethnicity, 21 identified themselves as Hispanic/Latino.

For analysis purposes, due to small sample size of each race and ethnicity the respondents were compared in two broader categories: Non-Hispanic White (69%) *vs*. URM (28%) and Non-Hispanic White (69%) *vs*. Hispanic/Latino (21%).

The majority of the respondents were females (81%), with an average age of 44 years (range 21-69 years, SD 9.8 years). The respondent's mean annual household income was high ($104,972). When controlling for outliers, the mean yearly household income was $91,787 (range $15,000-$200,000, SD 43,925). URM and non-Hispanic Whites reported fairly high annual house income and level of education with no differences observed. The majority of respondents belonged to the "middle economic class" (annual household $104,972), and had at least an Associate's degree. UMR respondents had a similar profile, with the mean annual household income being $108,037.64 and had at least an Associate's degree, or higher.

Twenty-five (25% of all participants) responders indicated that they have had their child participate in clinical trials, 28% of those were URM (n = 7). Descriptive statistics of clinical trial participants and non-clinical trial participants are shown in Table 1.

3.2. *Responders participation in clinical trials*

There were no associations between gender of respondent, race, ethnicity or URM classification and past participation in CTs (Race: χ^2 (1) = 0.795, p = 0.373) (Ethnicity: χ^2 (1) = 0.020, p = 0.887) (URM: χ^2 (1) = 0.718, p = 0.397). A statistically significant association was reported between "other" diagnosis and no participation in CT (χ^2 (1) = 10.68, p = 0.001). The diagnosis of FXS was significantly associated with past participation CTs ($p < 0.001$). A statistical significance for age of diagnosis and participation in CTs was found (z = –2.01, p = 0.045). The level of importance of being assigned to the placebo group (z = –2.27, p = 0.023) and the benefits from the study treatment (z = –2.49, p = 0.013) were associated with no participation (Table 2).

3.3. *Willingness to participate in CTs*

Fifty respondents, of which 30% (n = 15) were URM, indicated that they would be willing to participate in CTs. Twelve respondents, of whom 6 were URM (50%), indicated no willingness to participate in CTs. Thirty-eight of the total respondents were unsure whether they would participate in CT in the future; of those 14 were URM (36.8%).

To evaluate differences among future participation conditions (Yes-would participate in CT, No-would not participate in CT, and Don't know/unsure whether or not to participate in CT) the Kruskal Wallis test was used and revealed a significant effect on future participation in CTs on annual household income (H(2) = 7.24, p = 0.027). A post-hoc test using Mann-Whitney U tests with Bonferroni correction showed the significant differences in household income between those who reported willingness to participate and those who were not willing to participate in future CT ($p < 0.05$, r = 0.24) and between those who reported not participating and those who reported being unsure whether or not to participate in future CT ($p < 0.05$, r = 0.38) (lower income was associated with not willing to participate and unsure to participate). Furthermore, no willingness to participating in CTs and the amount of time involved were also found to be a significant association, (H(2) = 9.92, p = 0.007). The responders did significantly differ in their willingness to participate in future CT when stratified by annual household income, "other" diagnosis, and level of importance for amount of time commitment to CTs (Table 3).

The Wald criterion demonstrated that FXS diagnosis (p = 0.037) and age of diagnosis (p = 0.026) made a significant contribution to prediction. From the analysis, the odds ratio for diagnosis of FXS was 12 times as large and therefore, parents with a child diagnosed with FXS were 12 more times likely to have participated in CT.

Table 1. Description of responders participants and non-participants in clinical trials showing URM, age and annual household income

Group of respondents	All diagnosis	No. of respondents	URM	Age (25 and 75% percentiles)	Annual household income (25 and 75% percentiles)
Clinical trials participants (n = 25)	FXS	10	2	Median 43 years (32-56) Mean 42.74 years (+/- 1.449)	Median $86,000 Mean $112,801.33 ($27,828-$320,00)
	ASD	10	5		
	Asperger's	2	0		
	Learning Disabilities	1	0		
	ADHD	4	0		
	22q11.2 Deletion	1	0		
	Other*	2	0		
Non-Clinical Trial participants (n = 75)	FXS	4	2	Median 42 years (21-69) **n.s.* Mean 44.97 years (+/- 1.309) **n.s.*	Median $90,000 **n.s.* Mean $102,231 ($15,000-$400,000) **n.s.*
	ASD	20	7		
	Asperger's	14	6		
	Learning Disabilities	3	1		
	ADHD	10	5		
	22q11.2 Deletion	2	0		
	Down syndrome	1	0		
	Bipolar Disorder	2	1		
	Intellectual disability	1	1		
	Tourette syndrome	1	0		
	Compulsive Disorder	1	0		
	Other*	33	11		

Other* Undiagnosed-going through evaluation, neurotypical, neurotypical with attentional issues, Central Auditory Processing Disorder (CAPD), Dyscalculia-Math Disorder, Expressive/Receptive Language Disorder, depression, Borderline Personality Disorder, Ehlers-Danlos Syndrome, Septo-optic Dysplasia, Phenylketonuria (PKU) birth, schizophrenia, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS), dyslexia, pulmonary atresia, dwarfism, myotonic dystrophy, Long QT, Neurofibromatosis type I (NFI), Moebius syndrome, Tuberous sclerosis complex. **$n.s.$ no significant differences.

Table 2. Associations of participation in clinical trials

Variable	No. of Participants	No. of Non-participants	*p*
Fragile X diagnosis			
Yes	10	4	0.001*
No	15	71	
Other** diagnosis			
Yes	2	33	0.001*
No	23	42	
Level of importance–Child benefits from study treatment			
Not at all important	1	0	
A little important	3	2	
Somewhat important	6	10	
Very important	13	52	0.013*
Level of importance–placebo group			
Not at all important	11	12	
A little important	3	17	
Somewhat important	7	17	
Very important	2	17	0.023*

*Statistical significant at $p < 0.05$. Other**, Undiagnosed-going through evaluation, neurotypical, neurotypical with attentional issues, Central Auditory Processing Disorder (CAPD), Dyscalculia-Math Disorder, Expressive/Receptive Language Disorder, depression, Borderline Personality Disorder, Ehlers-Danlos Syndrome, Septo-optic Dysplasia, Phenylketonuria (PKU) birth, schizophrenia, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS), dyslexia, pulmonary atresia, dwarfism, myotonic dystrophy, Long QT, Neurofibromatosis type I (NFI), Moebius syndrome, Tuberous sclerosis complex

Table 3. Associations between participation and "other" diagnosis, ethnicity, income and time spent participating

Variable	Will participate (No)	Won't participate (No)	Unsure to participation (No)	*p*
Other diagnosis				0.004*
Yes	12	9	14	
No	38	3	24	
Total	50	12	38	
Ethnicity				0.057
Hispanic/Latino	12	5	4	
Not Hispanic/Latino	38	7	34	
Total	50	12	38	
Annual household income				0.027*
> 250,000	3	0	1	
150,000-249,999	8	0	3	
100,000-149,999	10	0	11	
60,000-99,999	15	4	8	
32,500-59,999	6	2	3	
23,051-32,499	1	2	1	
< 23,051	1	0	2	
Total	44	8	29	
Level of importance–Time				0.007*
Not at all important	6	1	1	
A little important	7	0	2	
Somewhat important	26	1	13	
Very important	9	4	15	
Total	48	6	31	

*Statistical significant at $p < 0.05$

3.4. *Level of satisfaction with participation in clinical trials*

Responders who had children participate in CTs (n = 25) were asked to rate how positive or negative their/ their child's experience was in form of a Likert scale of 'very negative' to 'very positive' (Figure 1). 62% reported a 'very positive' experience. In free text, several respondents amongst neurodevelopmental clinical trials participants reported that they, as well as the child, enjoyed working with the MIND staff and seeing improvements as the primary reason for their positive experience. As a typical example one respondent wrote: "My child enjoyed participating, but there were a lot of forms to complete".

3.5. *Motivational factors*

During the survey, respondents were asked to select the best reason(s) for their choice to participate or not to participate in CT. Among all respondents who were willing to participate in a clinical trial study, the top two motivating factors were to help find cures/treatments for neurodevelopmental disorders (77.2%) and relieve symptoms related to child's diagnosis (63.6%). Similar results were seen amongst the URM respondents (Figure 2). To consider participation in clinical trials, responders reported it being 'very important' to know more details about the trials; 78% participants indicated knowledge about how much their child/children would benefit from the study; 72% how much other people

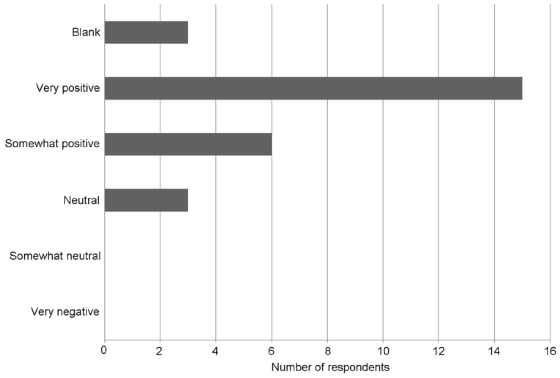

Figure 1. Level of satisfaction in clinical trials partipants.

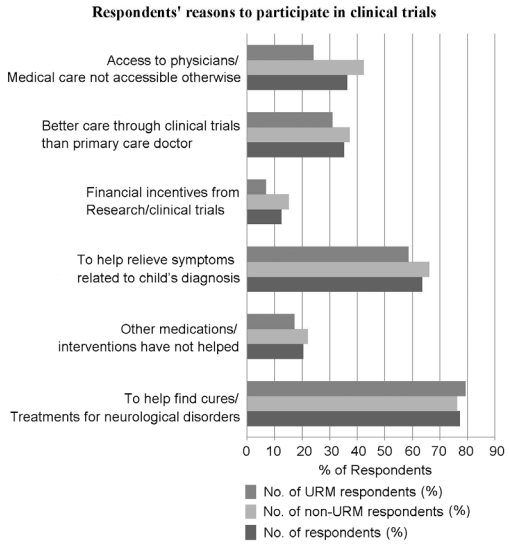

Figure 2. Respondents' reasons to participate in clinical trials.

would benefit from the study; and 70% for information about side effects. 64% of all respondents who were not willing or unsure to participate in CTs reported that lacking general knowledge/information regarding clinical trials was the main reason. In addition, 48% indicated time commitments and 32% indicated "other" reasons. Amongst URM respondents, 75% reported lack of general knowledge/information regarding clinical trials and 60% reported time commitment.

4. Discussion

Findings from this study yielded no association between gender, age, race and level of education (of both respondent and spouse/partner) in CTs participation. In our institute we have one of the only Spanish-speaking clinical trials clinic where personnel involved include coordinators, psychologists and physicians who are bilingual in Spanish. We also have the support of pharmaceutical companies to translate documents and standardized assessments in Spanish for a few of the clinical trials. There was a significant association between annual household income diagnosis and age of the diagnosis and CTs participation or willingness to participate. Low-income families were less likely to participate in CTs. Children who were diagnosed early in life and had diagnosis of FXS where more likely to participate in CTs. Older age at diagnosis and higher levels of importance of being assigned to a placebo group and expected benefits were significantly associated in parents who have not enrolled their children in CTs. This may suggest that education targeted to young parents in regard to diagnosis, benefits for treatment trials and benefits for participating, even when assigned to a placebo group, are necessary.

The observed significant difference in annual household income, between those who were willing and those who were not willing to participate, and between those who have not participated and those who were unsure about future participation, may suggest that the amount of time spent in CTs negatively affects economic status of these families. Therefore, those with lower income are less likely to participate or, consider participation. The work of low income earners may also be less flexible in allowing time off to participate in a clinical trial. Single parents may also find it impossible to participate in such trials. Findings from ASD studies report that URM families with a child with ASD experience more difficulties accessing services than Whites (*17-19*). However, the findings from our study reported otherwise. This could be caused by sampling bias, or the much lower number of respondents identified as URM compared to non-URM; also the URM sample were highly educated and had high household incomes; and finally, the responders were part of a referral center for neurodevelopmental disorders. We also found that a proportion of URM who have not been enrolled in CTs are willing to participate.

This study also highlights that Whites are sharing or facing the same participation barriers as URM, including knowledge and education in study benefits as well as side effects. This study also suggests that educational programs, decreasing time commitment and allowing more flexibility in the CTs schedules will increase participation among all the potential participants. Children who were not diagnosed with FXS and children diagnosed with "other" disorders were less likely to have participated in CTs. This is likely because the MIND Institute is a well-known center for CTs in FXS and exciting translational research has led to targeted treatment trials for this condition (*9*). Many of the responders to our survey included participants of these CTs. Pertinent to FXS, the mothers of FXS children are premutation carriers and may have many medical and psychological problems (*20*) that can be addressed during their children's CTs appointments, creating hybrid trials to help families rather than isolated family members. Efforts to increase minority participation in CTs should focus on ensuring infrastructure, meaningful outreach

and engagement efforts and access to health research for all groups, rather than solely attempting to change URM's attitudes.

There are limitations to performing questionnaire surveys and a greater depth of information could have been obtained by conducting either focus groups or interviewing participants. Thus, enabling the researcher to evaluate respondents' attitudes (negative or positive) and to identify other opinions and recommendations for services. In regards to income, studies have found that families with more than one child with neurodevelopmental disorders have more problems accessing medical care and have lower incomes, regardless of their education (*21*). In this study, the number of children with neurodevelopmental disorders in the families was not collected. In addition, not everyone reporting a low income indicated problems accessing health care as one of the reasons to participate or have participated in CTs. Further studies are necessary to understand and identify barriers for URM clinical trials participation, especially among children with neurodevelopmental disorders.

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