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Recruitment in a Pediatric Clinical Research Trial Targeting Underserved Populations: Efforts and Challenges

Kathy A. Ireland[1], **Aaron J. Manders**[1*], **Barbara E. Corkey**[2] **and Carine M. Lenders**[1]

[1]*Boston Medical Center, USA*

[2]*Boston University School of Medicine, USA*

[*]**Corresponding author:** Aaron J. Manders, MS, RD, LDN, Boston Medical Center, 88 E. Newton St.,Vose 507 Boston, MA 02118, USA, Tel: 6174143582; E-mail: aaron.manders@bmc.org

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Abstract

Introduction: To describe recruitment difficulties in a pediatric clinical trial targeting underserved pediatric obese populations.

Methods: We planned a 6-month randomized, double-blind, placebo-controlled clinical trial of glutamine vs. placebo, to reduce HOMA-IR and weight gain in obese adolescents. Participation required 5 visits at a research center at 8:00 AM. Cash incentives were provided at visits. After recruitment difficulties, study design was modified and recruitment efforts were intensified over a 14-week period. Subjects were recruited from Boston Medical Center's (BMC) pediatric outpatient clinics including the pediatric obesity program (NFL) which was staffed by members of the research team.

Results: 2002 adolescents were evaluated: 546 met BMI and age criteria. After further exclusions, 179 were eligible for a screening visit but only 4 attended. Additionally, 120 recruitment letters were sent to NFL patients, resulting in 4 attending a screening visit. Seven of the 8 adolescents attending a screening visit were from NFL, and 2 were randomized but subsequently lost to follow-up.

Discussion: Recruitment of pediatric patients from low-income and minority populations at BMC to a clinical trial is difficult. Challenges included strict inclusion/exclusion criteria and rigid appointment schedules. Existing patient-clinician relationships may increase recruitment. Future trials should use more flexible study designs.

Keywords: Pediatric obesity; Weight gain; BMI; Type II diabetes; Glutamine; Recruitment

Background

The dramatic rise of pediatric obesity, a condition typically associated with increased risk of type II diabetes (T2DM), is a critical threat to public health that especially affects minorities, [1,2] and results in high health care costs [3,4] and lower life expectancy [5,6]. Therefore, interventions aimed at delaying or preventing T2DM, especially those focusing on minorities, have the potential to dramatically improve the health of the US population and to reduce the burden of healthcare costs. Unfortunately, pediatric and minority populations have been historically under-represented in clinical trials despite efforts from institutions such as the National Institutes of Health (NIH) [7-11] while reasons for their under-representation remain equivocal.

Given the lack of clinical trials in pediatric and minority populations and the public health call to reduce risk of T2DM, we sought to conduct a 6-month randomized, double-blind, placebo-controlled clinical trial of pharmacological doses of glutamine versus placebo in obese Hispanic adolescents with a family history of T2DM and who receive care at an urban outpatient medical center. The purpose of the study was to determine the effect of pharmacological doses of glutamine on weight gain and HOMA-IR (insulin resistance) among Hispanic adolescents. Participation in the study required morning visits to a research center to obtain fasting bloodwork. Ultimately, the study was redesigned due to inability to recruit eligible participants. The objective of this article is to describe the barriers to participation observed in this trial of underserved pediatric minorities and provide recommendations for future clinical trials in such a population.

Methods

In 2008, one of the investigators on our team (CL) received a K23 career award from the NIH to conduct a double-blind, placebo-controlled clinical trial among adolescents from underserved areas to improve T2DM risk. We planned to screen a total of 264 obese teenagers ages 12 to 19 in order to identify 66 with high insulin levels (≥104.2 pmol/L) and randomize 56 to either glutamine or placebo supplements. The number of patients to be screened was largely based on preliminary data from a pilot lifestyle change study conducted in adolescents at Boston Medical Center (BMC) [12] which suggested that 20% of adolescents would have high fasting insulin levels (insulin ≥ 104.2 pmol/L), as defined based on a national study [13].

Participation in the study required five visits to the Clinical Transitional Science Institute (CTSI, formerly, General Clinical Research Center) over a 6-month period: a baseline visit to determine eligibility (week-4), a run-in visit to determine if the subject was able

to comply with study protocol (week-2), and randomization (week 0), mid-point (week 12), and final (week 24) visits. All visits were conducted at 8:00 AM so that fasting blood work could be obtained (Table 1).

What will happen during the visits?	Screening Visit	Run-in Visit	Randomization Visit	Midpoint Visit	Final Visit
	Week-4	Week-2	Week 0	Week 12	Week 24
Physical exam	X		X	X	X
Health questions	X		X	X	X
Drink-mix instruction/ assessment of intake		X	X	X	X
Fasting blood draw	X		X	X	X
DXA-scan			X		X
Food and activity questions	X	X	X	X	X
Urine tests			X	X	X
Incentive provided	$20	$30	$50	$50	$50

Table 1: Research participant initial schedule of visits.

However, given recruitment difficulties, the study design was altered multiple times over the following years. Initially, pediatric patients enrolled in the study were Hispanic individuals with a family history of T2DM. The inclusion criteria were then expanded to include individuals from all races/ethnicities with or without a family history of T2DM (Table 2). Despite this change, there was little improvement in recruitment. As a result, we decided to reevaluate and improve our recruitment strategies.

Inclusion Criteria	Exclusion Criteria
Age 12-19 years at enrollment	History of Type II Diabetes Mellitus
Fasting insulin ≥ 104.2 pmol/L	Prior drug treatment for diabetes or insulin sensitivity
BMI>95th percentile	Use of prescription strength glucocorticoids within 3 months before screening
Weight<300 pounds at randomization	History of a syndrome or medical disorder associated with significant obesity
Must speak English or Spanish	Weight loss of 5% or more within last 6 months
	Serum creatinine>91.5 μmol/L
	ALT or AST>1.5 μkat/L
	Total bilirubin>2.5 times the upper limit
	Past or current pregnancy
	Use of illegal/illicit drugs
	Inability to comply with study protocol
	Any other condition determined by clinical to be a potential risk for the subject

Table 2: Inclusion and exclusion criteria.

Recruitment efforts were intensified over a period of 14 weeks during the summer of 2010. A team of research assistants, a dietitian, student volunteers, a physician nutrition specialist, and a consultant with expertise in recruitment for studies targeting similar populations worked together to maximize recruitment of eligible patients in the outpatient clinics. Each week, the research team received a list of all patients scheduled for visits at pediatric outpatient primary care and specialty clinics at BMC the following week. The list included patients scheduled for visits in a variety of outpatient clinics including the pediatric obesity clinic, Nutrition and Fitness for Life (NFL). Investigators of this study were also clinicians at the NFL clinic.

Using the electronic medical record (EMR), the research team conducted chart reviews to determine the potential eligibility of patients with appointments in the various clinics based on criteria including age, medical history, and medications (Table 2). A member of the research team was assigned to meet eligible patients at their appointment and inform them of the study.

Eligible patients were given a pamphlet describing the study and provided with the opportunity to further discuss the study. Individuals interested in enrolling in the study were then scheduled for an appointment for a baseline/screening visit at the CTSI. The family received a reminder call the day before the visit with directions to the CTSI and instructions to arrive fasting. Parent consent and participant consent or assent was obtained based on age.

Additionally, letters informing potential subjects of the study were sent to patients ages 12-19 who attended the NFL clinic at BMC. Along with the letter, a study brochure and flyer were sent. Patients were encouraged to call the research team if interested in participating in the study. Interested and eligible patients who called were scheduled for a baseline/screening visit in the CTSI. All individuals also received incentives during the study: 20 dollars at signing the consent form, 30 dollars at the baseline visit, and 50 dollars at each of their following three study visits. This study was approved by the Institutional Review Board (IRB) at Boston University.

Results

A total of 2002 patients had outpatient appointments scheduled at BMC during the 14 week recruitment period. Of these, 27.3% (n=546) were eligible based on age and BMI. After further review, 67.2% (n=367) were found to be ineligible because of existing medical conditions (65%, n=239), medications (7%, n=27), or administrative reasons (27%, n=101). Administrative reasons for ineligibility included lack of information in the EMR or records marked as sensitive that could not be reviewed (Figure 1). Following these exclusions, a total of 179 patients were eligible to be approached at the time of their clinic visit (Figure 1).

Forty percent (n=73) of these patients (n=179) either cancelled or did not keep their appointment, which is consistent with the appointment cancellation/no-show rate of outpatient pediatric appointments at BMC. Another 32% (n=59) were not approached because an investigator was not available at the time of the appointment. This left only 26% (n=47) patients available to be approached by a member of the study team. Of the patients

approached, 9.3% (n=4) agreed to participate in the study. Three of the 4 (75%) who agreed to participate were patients of the NFL clinic.

Recruitment via letters sent to former NFL patients (n=120) yielded 4 (3.3%) additional interested patients. In total, 8 subjects attended a screening visit at the CTSI. Eighty-eight percent (n=7/8) of them had an existing or previous relationship with NFL.

At the baseline visit at the CTSI, 2 subjects were determined to be ineligible; one because of the start of a new medication and one because of inability to provide documentation to receive payment. Of the 6 subjects who had blood-work done, 33% (n=2) had a fasting insulin ≥ 104.2 pmol/L, which was higher than the expected rate of 20%. One subject was lost to follow-up prior to the first visit while the other subject was lost to follow-up before the final visit, resulting in a study completion rate of 0%.

With these findings, the study team decided that recruitment efforts had failed and a new course of action was needed to conduct the trial. As a result, the research team decided to recruit patients directly from the NFL clinic. However after 8 months, only one additional subject enrolled in the study. Anecdotally, potential subjects expressed an unwillingness and/or inability to attend 8:00 AM study visits on school days and the desire to continue lifestyle counseling in the NFL clinic while enrolled in the study.

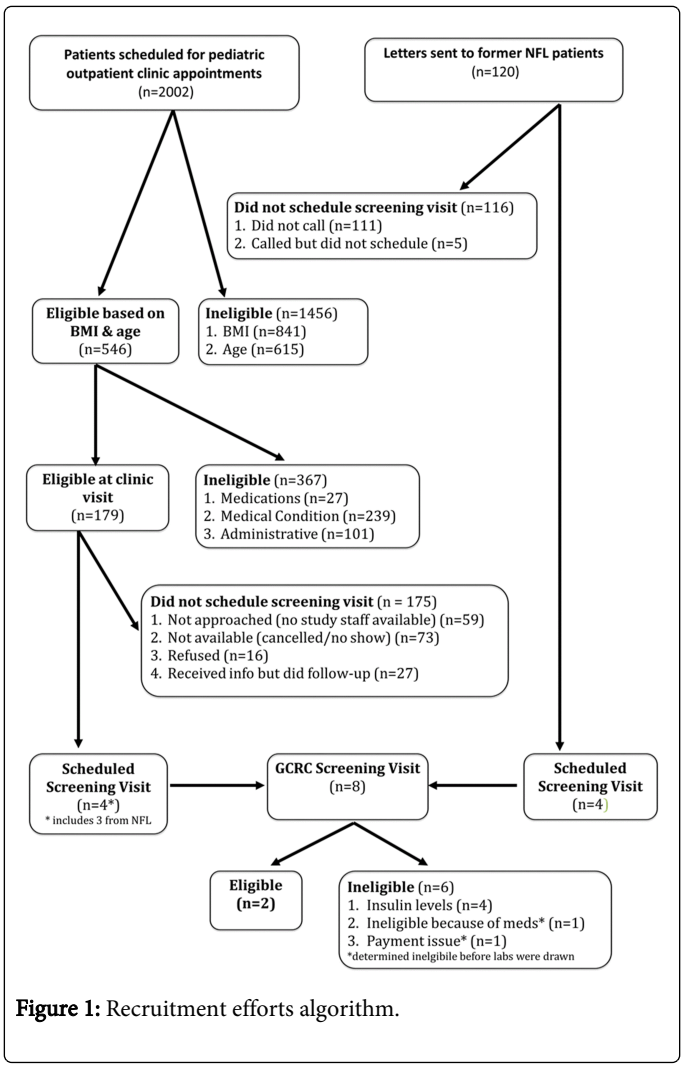

Figure 1: Recruitment efforts algorithm.

In April 2012 the study was stopped due to poor recruitment with the intention of changing the design of the study again. Following these changes, we received approval from the IRB to conduct the study at the NFL clinic, where patients received lifestyle counseling.

At this time, the study was no longer a double-blinded, placebo-controlled, randomized clinical trial and was now open labeled. Patients were either randomized to take glutamine supplements for 12-14 weeks while receiving NFL lifestyle counseling or not to take glutamine supplements while receiving NFL lifestyle counseling.

Notable changes in the study design included: 1) no minimum insulin level required, 2) recruitment from NFL clinic only, 3) shorter study duration and study visits taking place at the NFL clinic at the time of a regularly scheduled patient appointment, and 4) non-fasting blood work was drawn (Table 3).

A more accessible study with more flexible visits was restarted in April 2013. Since revising our study protocol, we have screened more than 300 potentially eligible participants in the NFL clinic over a 16-month period, of which 24 provided consent, 12 were enrolled, and 10 have completed the study (two were lost to follow up).

What will happen during the visits?	Randomization Visit Week 0	Midpoint Visit Week 4-6	Final Visit Week 12-14
Physical exam	X	X	X
Lifestyle counseling (provided by RD)	X	X	X
Demographic questions	X		
Drink-mix instruction/assessment of intake*	X	X	
Drug compliance review*		X	X
Non-fasting blood draw	X	X	X
Urine tests†	X	X	X
Incentive Provided	$50	$50	$100

*If randomized into the glutamine group; †Urine test provided at all visits for glutamine group, visits 1 and 3 for no-glutamine group

Table 3: Final clinical trial design.

Discussion

The main finding of this study is that the recruitment of pediatric patients from predominantly low-income and minority populations at BMC to a clinical trial is challenging, especially when schedules are rigid. Recruitment difficulties were exacerbated by strict inclusion/exclusion criteria that limited the pool of eligible participants and by limited staff resulting in the inability to contact all eligible participants during their clinic visits. We also found that an existing patient-clinician relationship may increase recruitment.

Our study observations confirm findings from other studies [14-17]. As observed in our study, many factors may create an environment that makes recruitment more challenging, including work demands, ability to travel, and limited access to child care [14,16]. One barrier identified in our study was the requirement to arrive at 8:00 AM for a fasting blood draw. This may be especially

difficult for single parents working multiple jobs and struggling to provide basic needs. Similarly, this time may be hard on adolescents who tend enjoy sleeping later, especially during summer months. Therefore, scheduling appointments after school and working hours may improve recruitment rates and retention of patients.

The initial focus of our study on Hispanic populations may have helped obtain a more homogeneous sample but may also have negatively affected our ability to recruit patients. Poor parental understanding [18] and language barriers have been found to be a discouraging factor for Hispanic participation [14]. More liberal eligibility criteria may help encourage recruitment but may also limit the strength of the conclusions. Unfortunately, both pediatric and minority populations are underrepresented in research, which is a cause of concern for discrimination [8,11,14,15,18]. Potential factors that may have contributed to underrepresentation of children in obesity trials include few funding opportunities and the requirement of more rigorous oversight [8,11]. Another factor is parental consent. Some authors report that parents from lower socioeconomic and education background are more likely to consent to a study [19,20] but their understanding of risk is lower [21,22] and their trust in research may thus be compromised [23-26]. Others [14,15] suggest that minorities are no less willing to participate in research. Therefore, efforts should be made to understand underrepresentation of pediatric patients and minorities.

Some authors [27] have shown higher recruitment rates in clinics where investigators already have an existing relationship with the potential research subjects, indicating that patients may be more willing to enroll in a study when they know an investigator personally, which is consistent with our findings. However, this dual relationship also raises concerns about coercion. Patients may confuse experimental care with standard of care. In that case, the investigators should work diligently to clearly explain both types of treatment [27] and to provide material that is written at an appropriate reading level [18]. Warner et al. [28] suggested that while challenging, conducting research in low-income and predominately minority populations is feasible but requires additional strategies. These authors used several strategies for aiding enrollment and retention including night and weekend appointments, ample study staff, and call centers to give patient appointment reminders. In our study, we were unable to approach 59 potentially eligible participants due to limited research staff resources. Conducting research in populations from minority and low income background requires creativity, time, and resources. Unfortunately, these requirements are scarce and funding for pediatric research remains limited [11]. Like Warner et al. [28] we believe that more funding is needed to improve recruitment in clinical trials in institutions targeting underserved pediatric populations.

In summary, our study recruitment challenges confirm previous findings of difficulties enrolling pediatric, minority, and underserved populations. However, we found that the location of the experiment and the flexibility of schedules were key to improving recruitment. More studies are needed to maximize participation of underserved populations to randomized clinical trials.

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