Study Title: Decisional Capacity and Informed Consent in Fragile X Syndrome

NCT number: 02465931

Most recent IRB approval date: June 11, 2018

Date of the document: November 8, 2018

Trial Design

We will use a two-arm, parallel design randomized control trial (RCT) with a 1:1 allocation ratio. Participants will be randomized into either the control or experimental group. Both groups will be exposed to the same informed consent content but delivered via different channels: a digital informed consent application (experimental) or paper informed consent/usual practice (control). The content of both versions of the informed consent describes the requirements for participating in a hypothetical clinical trial for a fake prescription drug for FXS. Both versions include IRB-required information (e.g., study procedures, study duration, compensation). The digital informed consent application does not meet all of the regulated technical requirements for electronic informed consent (i.e., the signature component).

Table 1. Overview of the study design, with details regarding how the variables differ across conditions.

Component	Control	Experimental
Delivery of information	Paper informed consent form paired with verbal overview of key points	Paper informed consent form paired with tablet-based tool which contains visual and audio components
Language	Complex (paper) and simplified (verbal overview)	Complex (paper) and simplified (tablet-based tool)
Exposure to information	Paper informed consent form will be sent to participant and family before data collection visit. They will be able to review as many times as they wish before visit. During visits, simplified overview of informed consent form will be provided in person just once.	Paper informed consent form will be sent to participant and family before data collection visit. They will be able to review as many times as they wish before visit. During visit, the participant can go through the tablet-based tool up to 3 times.
MacCAT questions	All questions will be asked after the disclosure information has been presented. Questions will have the same wording as experimental condition. Procedures will mimic MacCAT/flipchart (incorrect or partial credit will be given opportunity to answer question again after disclosure information is repeated).	All questions will be embedded within the vignettes/presentation of disclosure information. Use simplified wording for questions-similar to flipchart. Procedures will mimic MacCAT/flipchart (incorrect or partial credit will be given opportunity to answer question again after disclosure information is repeated).

	Multiple choice options rather than open-ended. Paper and pencil data collection	Multiple choice options rather than open-ended. Response data stored within tool and exported to dataset for analysis.

Participants

Up to 50 pairs of adolescents or adults (aged 14 or older) with FXS, a subset of 250 individuals who completed a battery of neurocognitive assessments (including IQ, reading abilities, autism and anxiety co-morbidities) between 2013-2016, will participate in the study.

Recruitment

Three primary methods will be used for recruitment: (1) recontacting the families who have participated in prior longitudinal assessment studies conducted by the research team; (2) recruiting through the FX research registry maintained by the University of North Carolina at Chapel Hill; and (3) announcing the research on the National Fragile X Foundation Web site. We have been highly successful in recruiting FX study participants, including a large national survey of over 1,000 families [45] so anticipate few problems in recruiting an adequate sample.

Inclusion / Exclusion

Eligibility will be determined by a person's scores on an initial assessment which included a standardized IQ and autism measure. Participants will be excluded if he or she (1) receives a score of 30 or less on the IQ measure; (2) receives a score between 31-40 on the IQ measure and has a diagnosis of autism with severe autism symptoms as noted on a standardized autism measure; or (3) is determined to have other behavioral challenges that would preclude their inclusion (e.g. mutism, severe aggression). These exclusion criteria cut offs were established to ensure a minimal level of comprehension and adaptive behavior for the study; IQs of 35 or below are indicative of severe intellectual disability.

Intervention

Control group. Participants randomized to the control group will be exposed to a paper consent form that covers the same informed consent information presented in the tablet-based application and mimics informed consent forms used for real clinical trials. The complex language that is typically used in current standard practice (i.e., *participation* vs. *take part*) will be retained in the paper version. The control group will be designed to mimic typical informed consent procedures, i.e., the verbal transmission of study information from a clinician to the individual and caregivers. To standardize this practice, we will develop a script that is verbally reviewed with control group participants including a simplified overview of the key information in the paper consent form.

Experimental group: Participants randomized to the experimental group will receive the paper consent form (the same form the control group participants received) and will also be exposed to the tablet-based application. Given that the digital application does not meet the requirements of electronic consent, the paper consent form will still be needed for documenting that informed consent was obtained.

Randomization

We will employ a stratified, block randomization method to assign participants to the control or experimental group. Two stratification variables will be used: Verbal IQ score (3 levels) and age (2 levels). Age was selected as a randomizing variable because children and adolescents under 18 are not able to provide informed consent, only assent, as their parents are their legal guardians. Verbal IQ was selected as a second variable because we had a small sample size and wanted to control for any possible effects on the outcome variables. However, we could have also chosen to account for any possible group differences based on IQ through statistical analyses. Given that enrollment for the RCT will be

done on a rolling basis, a 10 block, 2 group design will be used. Thus, we will randomize 10 participants at a time into either the control or experimental group. We will utilize a random number generator (www.randomizer.com) to make the assignments.

Blinding

Due to the nature of the study, participants and data collectors were not blinded to group assignment.

Study Setting and Data Collection Procedures

Each study session will occur in the individual's home and will be videotaped to allow subsequent coding of individual engagement in the decisional process. Approximately 10 days prior to the visit, the participant and/or their primary caregiver will be sent the standard paper consent form for a hypothetical clinical trial. All participants, including parents and caregivers, will be informed that the clinical trial is hypothetical. Participants will be asked to review the consent form as they would any research consent from.

On the day of the visit, parents and individuals with FXS who are their own legal guardian will be asked to complete a 5- to 10-minute pre-test to assess their/their child's belief and attitudes about participating in clinical trials. Pre-test items included questions such as the participant's possible reasons for participating in clinical trials, the likelihood of participating, and who they think should make the decision about enrolling in a trial (full list of domains in Study Outcomes section below). Participants will then complete either the experimental or control group informed consent procedure. Both the control and experimental groups will be asked the modified MacCAT examination items throughout the informed consent process to assess decisional capacity. The questions are identical for each group. After the informed consent procedure, all participants will again be asked to complete the post-test questions about their beliefs and attitudes about clinical trials

Study Outcomes

The following measures will be collected as part of the study protocol:

- Time spent with decision aid or in discussion with research assistant
- Perceptions about reasons to participate in trials (e.g., altruism; pre- and post-test item)
- Likelihood of enrolling in a clinical trial (pre- and post-test item)
- Preferred level of involvement in the decision (pre- and post-test item)
- Self-efficacy related to decision-making ability (pre- and post-test item)
- Level of engagement in the decision-making process (pre- and post-test item)
- Satisfaction with the decision (post-test only)
- Perceived value of the educational information provided (post-test only)
- Session analytics, including time on page and session duration

Participant Timeline

Pre-test measures, the intervention or control condition, and post-test measures will all be conducted on the same day during an approximately 1-hour study session. The pre-and post-test measures will take approximately 15 minutes to complete and the control and intervention condition will last approximately 30 minutes. No additional follow-up is planned.

Statistical Methods

In the analyses, we will examine the effect of the app on decisional capacity, controlling for sociodemographic characteristics and severity of delay. We will first conduct bivariate analyses comparing decisional capacity, decision making preferences, and likelihood of trial participation across the two study groups (tablet vs. standard procedure), using chi-square tests for categorical outcomes

and t-tests for continuous outcomes. In addition, we will conduct multiple regression models to compare study outcomes by study group after controlling for demographics and severity of developmental delay. Linear regression models will be conducted for continuous outcomes (e.g., decisional capacity scores, preferences) and logistic regression models for categorical outcomes (e.g., likelihood of participating in a hypothetical trial). Within these models, we will test for interactions between study group and demographic characteristics to identify differential impact of the intervention on particular subgroups. For example, testing an interaction between study group and severity of delay would allow us to determine if the tablet-based intervention is more or less successful among more impaired participants.

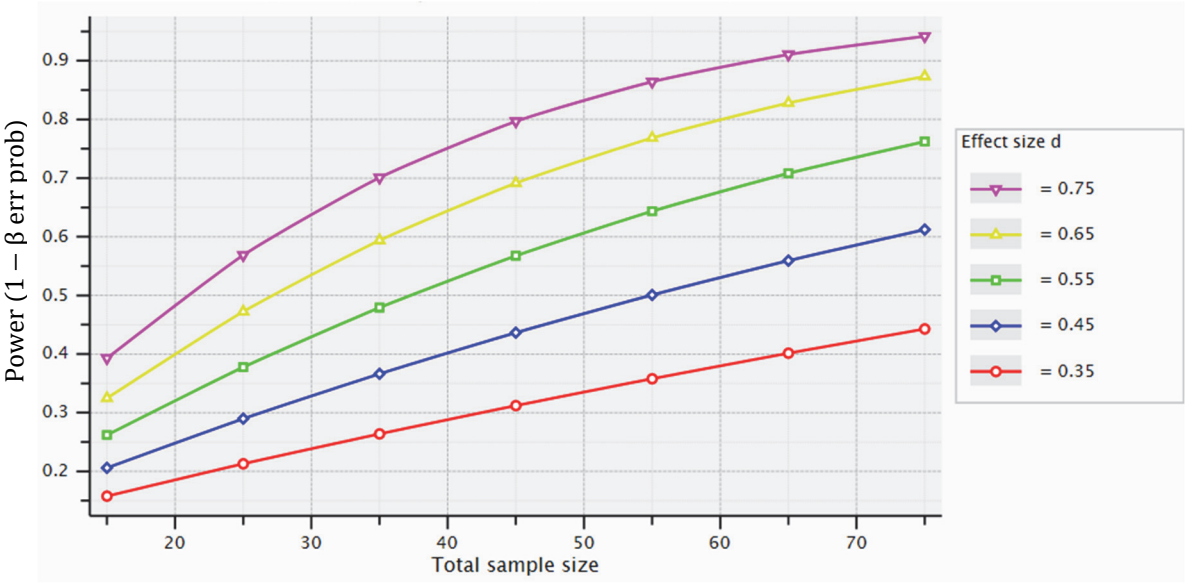
Power Analyses

To determine the recommended sample size, we have conducted a power analysis using a between-subjects design (i.e., participants are randomized to control or experimental group). See Figure 1 below. With a sample size of 70 (35 participants per group), we will have 90% power to detect an effect size of .75.

Figure 1. FXS Power Analysis

t tests – Means: Difference between two independent means (two groups)

Tail(s) = One, α err prob = 0.05, Allocation ratio N2/N1 = 1



Ethics and Confidentiality

This research protocol was reviewed and approved by two Independent Review Boards from the University of North Carolina Office of Human Research Ethics (IRB Number: 13-1128) and RTI International Office of Research Protection (0281200.276). This study has been registered with ClinicalTrials.gov (NCT02465931).