Study Protocol and Statistical Analysis Plan

Title of Study: Web-based Resource for Children and Adolescents About Clinical Research
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Study Protocol

Objectives:

Clinical trials with pediatric populations are needed in order to ensure the treatments are tested with and work for children and adolescents. However, there are a number of barriers to recruitment and enrollment of children and adolescents. *DigiKnowIt News: Teen* (*DKIN: Teen*) is an interactive educational website designed to educate adolescents (aged 12 to 17) about pediatric clinical research and equip them with information to make informed decisions about participation. The main objective of the study is to test the effectiveness of *DKIN: Teen* related to factors that could influence participation in pediatric clinical trials. This study will examine if *DKIN: Teen* increases adolescents' knowledge about clinical trials, adolescents' and parents' positive attitudes and beliefs towards clinical trials, adolescents' self-efficacy about the decision to participate in a clinical trial, adolescents' and parents' likelihood and willingness to participate in a clinical trial, and adolescents' and parents' communication quality, as well as reduce adolescents' fears associated with research participation.

Design:

The study is a parallel group randomized controlled trial with a 1:1 allocation ratio and superiority framework to test the efficacy of *DKIN: Teen* for improving factors related to clinical trial participation among parent-adolescent pairs. The randomized controlled trial will be conducted online at two time points: 1) baseline/pre-test and 2) post-test (one week after pre-test). The study questionnaires will be programmed into an online data collection system and the intervention itself is also completed online.

Participants will be randomized, stratifying based upon gender (boy; girl; non-binary), race/ethnicity (white and not Hispanic/Latino; nonwhite and/or Hispanic/Latino), and health status (health;/chronic illness), to one of two conditions: 1) intervention (pairs will receive access to *DKIN: Teen* right away) or 2) wait-list control (pairs will not have access to the intervention between pre-test and post-test assessments; after completing the post-test questionnaire, pairs will be given the option to review *DKIN: Teen*).

Participants are randomized and enrolled based on: 1) time study forms (e.g., consent) were completed, 2) confirmation of email addresses, and, 3) their reported demographics collected in the eligibility screener questions (described below in the Sample and Recruitment section). One of the leading investigators will generate the allocation sequences using a random number generator in Excel. After eligibility is determined, the other leading investigator will assign participants to condition (either intervention or wait-list control) according to those sequences and then enroll participants in the study. The allocation sequence will be stored in a folder on a secure, password-protected server and will only be accessible by the leading investigator who created the sequence. All participants will be assigned a unique ID number that will be associated with their data in place of a name.

Methods:

Sample and Recruitment. Parent-adolescent (ages between 12 and 17 years) pairs will be recruited for the study. To be eligible to participate in the study, the following criteria must be met: a) adult participant is a parent or legal guardian of adolescent participant; (b) adolescent participant is 12-17 years of age; (c) parent-adolescent pair has access to a computer or tablet with internet connection; (d) ability to speak and read in English; and (e) no current or previous participation in a clinical trial after kindergarten. This study will investigate if the *DKIN: Teen* website improves attitudes and decision-making of adolescents who have not yet participated in a clinical trial and thus, excludes those who have already had the experience of being in a clinical trial. Parent-adolescent pairs will be recruited from across the United States. A study recruitment website will contain information about *DKIN: Teen* and the research study that interested parent-adolescent pairs can review. Parent-adolescent pairs will also be recruited via flyers and with the help of consultants who have access to networks of pediatric groups and pediatric health organizations, as well as help from other health advocacy and parent groups. Study flyers will also be shared via email and social media (e.g., Facebook) and via PeachJar, a digital flyer service within school districts. Efforts will be made to ensure about equal samples of boys and girls as well as healthy adolescents and adolescents with varying chronic diseases/disorders between the intervention and wait-list control groups. The sample will represent diversity in ethnicity and race.

Procedure. Interested parents and adolescents will visit the recruitment website to learn more about the study and respond to the study eligibility screening questions. In order to be eligible to participate in the study, a parent-adolescent pair must have access to computer or tablet with internet connection and English fluency. In addition, the adolescent participant must be within the ages of 12-17 and have NOT participated in a clinical trial. Parents will be asked to indicate their child's race, ethnicity, gender, and health status (healthy/have chronic illness) to assist in ensuring a diverse sample of participants. Parents will also be asked to indicate their own gender, race, and ethnicity. Parents will be notified onscreen immediately if their child is eligible to participate in the study, and if so, will be given access to online permission, consent, and assent forms. They will be instructed to review the forms together so they can decide about participation. Parents will complete an online consent form for their own participation and permission form for their child's participation and the adolescent will be asked to complete an online assent form. Interested participants who decide to complete the forms will be told that in an attempt to have a diverse sample, they may not be invited to participate. Parent-adolescent pairs can contact the research team about any questions they might have after they have reviewed and signed the forms.

The permission, consent, and assent forms will describe the goals of the study, as well as the minor potential risks and the benefits of participation. Permission, consent, and assent forms will also state the participant may discontinue their participation at any time. Parents will be provided with the option to receive text messages related to their study participation in addition to receiving emails. Language in the adolescent assent will be appropriate for the age group in the study, in order to ensure that they understand all procedures. Potential parent-adolescent pairs will be provided with the contact information of the researchers and may contact them to ask any questions they may have about the study. Only parent-adolescent pairs with completed study forms will be permitted to participate in the study. Parent-adolescent pairs will read the

permission, consent, and assent forms and provide online permission, consent and assent by typing their names into a text box, providing contact information, and clicking a button to indicate permission and consent (parent) or assent (adolescent), rather than providing us with a signed hard copy of the forms. They will have the option to download and/or print the forms to retain a copy for their files.

iRT project staff will determine whether or not the address the parent has provided for the pair in the informed consent forms is real using a Google map search. Eligible parent-adolescent pairs who have completed all study forms (parental consent and permission and adolescent assent) will be invited to participate by project staff members if there is space for them in the study depending on their demographic characteristics. Parents will receive a welcome email that will provide more information on the timeframe and tasks for the study. Approximately equal numbers of male/female adolescent participants and chronically ill/healthy adolescent participants will be randomly assigned to condition (*DKIN: Teen* OR wait-list control). The goal is to enroll a diverse sample of adolescents with respect to race and ethnicity.

When the study starts, parent-adolescent pairs will receive an enrollment email (and text message - if the family has opted-in to receive text messages) from iRT's study management system via the parent's email address (and phone) with a link for the participating parent to complete the online parent pretest questionnaire within one week. This enrollment email (and text) will also indicate that the parent will receive a second message with a unique link for their adolescents to use to complete the online teen pretest questionnaire within one week. Completion of the pretest questionnaires may take up to 30 minutes for adolescents and 15 minutes for parents. Upon completion of the pretest questionnaires, parent-adolescent pairs will see a message at the end of the questionnaire indicating that the parent will receive an email (and text) regarding the pair's next steps in the research study.

- Pairs in the intervention group will receive an email (and text) that they are able to access *DKIN: Teen* immediately with instructions on how to access and review *DKIN: Teen*. The *DKIN: Teen* website is expected to take about up to 2 hours to fully complete and can be done in more than one sitting.
- Pairs in the wait-list control group will receive an email (and text) telling them that they will be asked to complete another set of questionnaires in about one week. Participants in the wait-list control group will not have access the *DKIN: Teen* during this time and will receive business as usual, which in this case is no clinical trial information. The wait-list control group will later receive access to *DKIN: Teen* once they have completed the posttest questionnaires.

Project staff members will monitor *DKIN: Teen* website usage through iRT's Learning Management System (LMS). Approximately one week after completing the pretest questionnaire, participating parents will receive an email (and text) with a link for the parent to access the online parent posttest questionnaire to be completed within one week. This parent email (and text) will also indicate that the parent will receive another message with a unique link for their adolescents to use to complete the online teen posttest questionnaire within one week. Completion of the posttest questionnaires may take up to 30 minutes for adolescents and 15 minutes for parents. Participants in the intervention group will receive the Consumer Satisfaction Questionnaire at the end of their posttest questionnaire. Completion of the Consumer Satisfaction Questionnaire may take approximately 15 minutes.

Participants in the wait-list control group will have the option of reviewing *DKIN: Teen* after their posttest data have been collected. After a week, the wait-list control group will have the opportunity to complete the Consumer Satisfaction Questionnaire about *DKIN: Teen*. Completion of the Consumer Satisfaction Questionnaires by participants in the wait-list control group is optional and those participants will not receive an incentive for completing these questionnaires. Parents (in the wait-list control group) will receive an email (and text) with a link for the parent to access the online parent Consumer Satisfaction Questionnaire to be completed within one week. This email (and text) will also indicate that the parent will receive another message with a unique link for their adolescents to use to complete the online teen Consumer Satisfaction Questionnaire within one week.

Participants will receive automatic email (and text) reminders from the study management system if they have not completed the questionnaires or not accessed *DKIN: Teen*. The research team will also call a parent or send a check-in email to a parent if there is no response following the automatic reminder. Incentives for completing the pretest questionnaires and for completing the posttest questionnaires will be physically mailed to parent-adolescent pairs using the address provided on their study forms. At the end of the study, responses on the online questionnaires will be downloaded from the online data collection system and saved on a secure, password-protected network in preparation for statistical analyses.

Measures.

Adolescents

Knowledge. This measure has been created for the purposes of this study. Adolescents will respond to 27 questions that assess their factual knowledge about clinical research (e.g., "What is a clinical trial?"). Questions are in multiple choice format (some questions have multiple correct answers), and the total score could range from 0-53 correct. Higher scores indicate more knowledge about clinical research.

Attitudes about clinical trials. This measure was originally adapted from Madsen and colleagues (2002) and used in Parker et al (2022). The items are slightly adapted. Adolescents will be asked to respond to 6 questions that assess their positive attitudes about clinical trials (e.g., How do you feel about teens participating in clinical trials?; 1=Not good at all; 2=Not very good; 3=Not sure; 4=Good; 5=Very good; $\alpha = 0.83$). Responses will be averaged and the minimum scale score is 1 and the maximum scale score is 5. Higher scores indicate more positive attitudes toward clinical trials.

Beliefs about clinical trials. Adolescents will be asked to respond to 5 questions about their beliefs about pediatric clinical research (e.g., I believe that clinical trials can help teens; 1=Strongly disagree; 2=Disagree; 3=Unsure; 4=Agree; 5=Strongly agree; $\alpha = 0.78$; Parker et al., 2022). Responses will be averaged and the minimum scale score is 1 and the maximum scale score is 5. Higher scores indicate more positive beliefs about clinical trials.

Self-efficacy to communicate. This measure was originally adapted from Bandura (2006) and used in Parker et al. (2022). The items were slightly adapted and split into two scales (self-efficacy to communicate and self-efficacy to gather information, below). Adolescents will be

asked to respond to 10 questions about their self-efficacy for making decisions about clinical trial participation specific to communicating about clinical trials (e.g., Tell a doctor or researcher if I want to stop the clinical trial; 1 = I cannot do it at all; 5 = I know I can do it; α = 0.89; Parker et al., 2022). Responses will be averaged and the minimum scale score is 1 and the maximum scale score is 5. Higher scores indicate more self-efficacy about communication.

Self-efficacy to gather information. This measure was originally adapted from Bandura (2006) and used in Parker et al. (2022). Adolescents will be asked to respond to 9 questions about their self-efficacy for making decisions about clinical trial participation specific to gathering information about clinical trials (e.g., Ask a doctor or researcher questions for more information about clinical trials; 1 = I cannot do it at all; 5 = I know I can do it; α = 0.89; Parker et al., 2022). Responses will be averaged and the minimum scale score is 1 and the maximum scale score is 5. Higher scores indicate more self-efficacy about gathering information.

Confidence for participating in clinical trials. Adolescents will also be asked to respond to additional items to measure youths' confidence for participating in clinical trials (e.g., "I know what rights I have in a clinical trial."; 1=Strongly disagree; 2=Disagree; 3=Unsure; 4=Agree; 5=Strongly agree; α = 0.77; Parker et al., 2022). Responses will be averaged and the minimum scale score is 1 and the maximum scale score is 5. Higher scores indicate more confidence in participating in clinical trials.

Procedural fears. Adolescents will be asked to respond to 4 questions related to their perceptions of fear or anxiety about different types of medical procedures, including getting a needle in the arm, injection in the leg, getting a scan, and taking new medicine, on a 5-point Likert scale (1 = Not at all afraid or anxious, 2 = Somewhat afraid or anxious, 3 = Moderately afraid or anxious, 4 = Very afraid or anxious, 5 = Extremely afraid or anxious). Responses will be averaged and the minimum scale score is 1 and the maximum scale score is 5. Higher scores indicate more fear about procedures. The original measure has strong reliability and validity (Kowalsky et al., 2014).

Likelihood of participation in clinical trials. Adolescents will be asked to respond to one question about the likelihood of participating in a clinical trial (i.e., "If you were asked to be in a clinical trial, how likely would you be to participate?") using a 5-point Likert scale (1 = Not likely at all; 2 = Not very likely; 3 = Not sure; 4 = Likely; 5 = Very likely). Responses will be averaged and the minimum scale score is 1 and the maximum scale score is 5. Higher scores indicate greater likelihood of participation in a clinical trial.

Likelihood of fear preventing participation in clinical trials. Adolescents will be asked to respond to one question about the likelihood of their fear preventing them from participating in a clinical trial (i.e., "How likely is it that your fearful or anxious feelings could stop you from participating in a clinical trial in the future?") using a 5-point Likert scale (1 = Not likely; 2 = Somewhat likely; 3 = Moderately likely; 4 = Very likely; 5 = Extremely likely). Responses will be averaged and the minimum scale score is 1 and the maximum scale score is 5. Higher scores indicate greater likelihood of fear preventing participation in a clinical trial.

Familiarity with clinical trials. Adolescents will be asked to respond to one question about their familiarity with clinical trials ["How much do you know about pediatric clinical trials (research studies with children under 18)?"; 1 = I don't know anything; 2 = I know a little about them; 3 = I know some things about them; 4 = I know a lot about them; 5 = I know all there is to know about them]. Responses will be averaged and the minimum scale score is 1 and the maximum scale score is 5. Higher scores indicate greater familiarity with pediatric clinical trials.

Willingness to participate in a clinical trial. Adolescents will review five research protocols related to a fictitious disease ('meditis') and respond to a question about their willingness to participate in each research study (e.g., If you had meditis, would you agree to enroll in this study?; 1 = Definitely not to 7 = Definitely yes). Responses will be averaged across the five protocols and the minimum scale score is 1 and the maximum scale score is 7. Higher scores indicate greater willingness to participate in the research studies. This measure was adapted from Brody and colleagues (2005).

Quality of parent-adolescent communication. Adolescents will be asked to respond to 8 questions related to their perceptions of their relationship quality and communication with their parents (e.g., "My parent gives me good advice."; "When talking to my parent, he/she tries to understand my point of view."; 1 = Strongly disagree; 2 = Disagree; 3 = Agree; 4 = Strongly agree). Responses will be averaged and the minimum scale score is 1 and the maximum scale score is 4. Higher scores indicate more positive perceptions of relationship quality. This measure has strong reliability (Mallett et al., 2011).

Parents

Attitudes about clinical trials. Parents will be asked to respond to 6 questions that assess their positive attitudes about clinical trials (e.g., How do you feel about teens participating in clinical trials?; 1=Not good at all; 2=Not very good; 3=Not sure; 4=Good; 5=Very good). Responses will be averaged and the minimum scale score is 1 and the maximum scale score is 5. Higher scores indicate more positive attitudes toward clinical trials. This measure was adapted from Madsen and colleagues (2002) and used in Parker et al (2022).

Beliefs about clinical trials. Parents will be asked to respond to 5 questions about their beliefs about pediatric clinical research (e.g., I believe that clinical trials can help teens; 1=Strongly disagree; 2=Disagree; 3=Unsure; 4=Agree; 5=Strongly agree). Responses will be averaged and the minimum scale score is 1 and the maximum scale score is 5. Higher scores indicate more positive beliefs about clinical trials. This measure was adapted from Parker et al (2022).

Likelihood of participation in clinical trials. Parents will be asked to respond to one question about the likelihood of allowing their child to participate in a clinical trial (i.e., "If your child were asked to be in a clinical trial, how likely would you be to let them participate?") using a 5-point Likert scale (1 = Not likely at all; 2 = Not very likely; 3 = Not sure; 4 = Likely; 5 = Very Likely). Responses will be averaged and the minimum scale score is 1 and the maximum scale score is 5. Higher scores indicate greater likelihood of allowing child to participate in a clinical trial.

Likelihood of fear preventing participation in clinical trials. Parents will be asked to respond to one question about the likelihood of their fear preventing them from allowing their child to participate in a clinical trial (i.e., "How likely is it that your fearful or anxious feelings could stop you from allowing your child to participate in a clinical trial in the future?") using a 5-point Likert scale (1 = Not likely; 2 = Somewhat likely; 3 = Moderately likely; 4 = Very likely; 5 = Extremely likely). Responses will be averaged and the minimum scale score is 1 and the maximum scale score is 5. Higher scores indicate greater likelihood of fear preventing their child's participation in a clinical trial.

Familiarity with clinical trials. Parents will be asked to respond to one question about their familiarity with clinical trials ["How much do you know about pediatric clinical trials (research studies with children under 18)?"; 1 = I don't know anything; 2 = I know a little about them; 3 = I know some things about them; 4 = I know a lot about them; 5 = I know all there is to know about them.]. Responses will be averaged and the minimum scale score is 1 and the maximum scale score is 5. Higher scores indicate greater familiarity with pediatric clinical trials.

Willingness to participate in a clinical trial. Parents will review 5 research protocols related to a fictitious disease ('meditis') and respond to questions about their willingness to let their child participate in each research study (i.e., "If your child had meditis, would you agree to enroll them in this study?"; 1 = Definitely not to 7 = Definitely yes). Responses will be averaged across the five protocols and the minimum scale score is 1 and the maximum scale score is 7. Higher scores indicate greater willingness to allow their child to participate in the research studies. This measure was adapted from Brody and colleagues (2005).

Quality of parent-adolescent communication. This measure was adapted from Barnes & Olson (Barnes & Olson, 1982) and used in Scull et al. (2022). Parents will be asked to respond to 16 questions regarding their perceptions of the quality of communication with their adolescent (e.g., "If my child were in trouble, she/he could tell me"; 1 = Strongly disagree, 2 = Disagree; 3 = Agree; 4 = Strongly agree; $\alpha = 0.85$). Responses will be averaged and the minimum scale score is 1 and the maximum scale score is 4. Higher scores indicate more positive perceptions of relationship quality.

Implementation

Dosage. iRT's Learning Management System will record the amount of time that adolescents and parents spend on the *DKIN: Teen* website components and the specific components reviewed.

Consumer Satisfaction

Consumer Satisfaction Questionnaire for Adolescents *(CSQ-A)* will assess teen's satisfaction for four sections of *DKIN: Teen* (Investigations, Comic Books, Spotlight Videos, and Parent-Teen Shared Decision-Making) in terms of: (1) content (e.g., The Spotlight Videos were interesting to me.); (2) format (e.g., I liked the videos I saw in the Investigations.); (3) usability (e.g., I could figure out how to make the Comic Books work.). Overall quality will also be assessed (e.g., I would tell a friend who wanted to know about clinical trials about the

DigiKnowIt News website.). Participants will rate each item on a 5-point Likert scale (1 = Strongly disagree; 5 = Strongly agree). Adolescent participants will also be asked to provide open-ended feedback.

Consumer Satisfaction Questionnaire for Parents *(CSQ-P)* will assess parents' satisfaction with the Parent-Teen Shared Decision-Making section of *DKIN: Teen* in terms of (1) content, (2) format, and (3) usability. Participants will rate each item on a 5-point Likert scale (1 = Strongly disagree; 5 = Strongly agree). Parents will also be asked to provide open-ended feedback. Finally, parents will complete 12 items related to the acceptability (AIM), appropriateness (IAM), and feasibility (FIM) of the Shared Decision-Making section, using a 5-point Likert scale (1 = Completely disagree; 5 = Completely agree; Weiner et al., 2017).

Statistical Analysis Plan

Data will be analyzed using SAS 9.4.

Preliminary analyses. Preliminary analysis will include a test of equivalency between groups on demographic background characteristics using chi-squared analyses for categorical variables and t-tests for continuous variables. Psychometric analyses will be conducted to examine the reliability, validity, and distributions of key variables. Handling variables with poor reliability or validity will include modification or elimination of such variables from the analysis data sets. Variables with noticeably skewed distributions will be transformed or categorized to reduce the impact of non-normality on subsequent analyses. Descriptive statistics will also be conducted to examine the distributions, correlations, means, and standard deviations of the adolescent and parent outcome variables (listed in the Measures section).

Main analyses. Multiple regression analyses will be used to investigate differences in outcomes (i.e., knowledge about clinical research, attitudes and beliefs towards pediatric clinical trials, self-efficacy in making decisions related to clinical trials, likelihood and willingness to participate in clinical trials, procedural fears, communication quality) using condition (intervention; wait-list control) as the independent variable of interest. A series of multiple regressions will be used to examine if using *DKIN: Teen* impacts the post-test knowledge, attitudes, efficacy, likelihood and willingness to participate, fears, and communication quality of participants. Pre-test scores for each outcome will be included as predictor variables; thus, outcome variable means will be reported as adjusted post-test scores. Demographic variables found to be non-equivalent between groups will be included as covariates in these models. The effect sizes will be calculated by dividing the appropriate contrast parameter by the sample standard deviation of the outcome. If unexpected results are obtained, then the process data recorded by the LMS (e.g., time spent on parts of *DKIN: Teen* website) and measures of satisfaction will be examined to investigate whether differing dosage or satisfaction levels can explain unexpected patterns of findings. Additional analyses will examine subpopulations and test age, gender, and health status (chronic illness/no illness) as potential moderators of the effectiveness of *DKIN: Teen*.

Analyses will be intention-to-treat, so that participants who do not adhere to the protocol are still included in the analysis in their assigned condition. Missing data will be handled in each

outcome analysis with an appropriate imputation method, and estimates and standard errors will be adjusted for imputations, if warranted.