

Title: **Examining how children benefit from the assent process for research decisions**

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ABBREVIATIONS AND DEFINITIONS OF TERMS

IRB	Institutional Review Board
CTO	Clinical Trials Office
REDCap	Research Electronic Data Capture
AE	Adverse Event
DMIS	Decision Making Involvement Scale

ABSTRACT

Context: (Background)

Debates about the meaning and requirements for child assent to research participation permeate the bioethics, medical, and psychology literatures, but empirical research in this area is in its infancy. The assent process is important for conforming to research regulations but can also be used to enhance children's sense of self-efficacy in health care settings. Optimizing children's roles in research decision making is critical, especially during pre-adolescence and adolescence, when children begin to strive for and acquire more decision making independence.

Objectives: (primary and important secondary objectives)

The primary objective of this research is to examine the benefits of children's involvement in decisions about clinical trial enrollment and whether these benefits vary based on child demographic and psychosocial characteristics. In other words, do some children benefit more from involvement than others?

Study Design:

This cross-sectional study will assess families within 10 days of having made an actual decision about clinical trial enrollment for the treatment of a chronic condition in the child.

Setting/Participants:

Participants will be 180 children (and their parents) who made a decision about whether to enroll the child in a Phase II, III, or IV clinical trial involving an intervention related to a chronic condition (e.g., cystic fibrosis, juvenile idiopathic arthritis, diabetes). Children with a cancer diagnosis will be excluded, due to the unique features of clinical research in this population. In two-parent families, both parents will be invited to participate, but participation by both parents will not be required. *Inclusion criteria:* 1) Parents and children are English-speaking, 2) Child between 10 and 17 years-old. *Exclusion criteria:* 1) Child has no knowledge that a decision about clinical trial enrollment was made, 2) Child is unable to complete phone interview due to health status or functional impairment, 3) Child has a diagnosis of cancer, 4) Child has diagnosis of mental retardation or pervasive developmental disorder, 5) Child had psychiatric hospitalization in the past year.

Study Interventions and Measures:

There is no intervention. Main outcomes are children's perceptions of the fairness of the decision-making process and children's self-efficacy.

TABLE 1: SCHEDULE OF STUDY PROCEDURES

Procedure	Screening and Study Visit (1 visit only)
Informed Consent/Assent	X
Review Inclusion/Exclusion Criteria	X
Verbal administration of questionnaires to child	X
Verbal administration of questionnaires to parent	X

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

Debates about the meaning and requirements for child assent to research participation permeate the bioethics, medical, and psychology literatures, but empirical research in this area is in its infancy. The assent process is important for conforming to research regulations but can also be used to enhance children's sense of self-efficacy in health care settings. Optimizing children's roles in research decision making is critical, especially during pre-adolescence and adolescence, when children begin to strive for and acquire more decision making independence. Prior research on child assent has been based on a model that focuses on cognitive capabilities; this research examines children's understanding of the elements of research and the factors that influence their understanding. A second model of child assent focuses on the relational context of children's decision making. This model recognizes that decision making typically occurs in a family context and attends to the role of collaborative decision making in normative development. The relational model focuses not on *who* makes the decision, but on *how* parents and children talk about it. It reflects the view that children can be involved in decisions in various ways and that parents play an important role as sources of support and advice across the child's development. The primary objective of this research is to examine the benefits of children's involvement in decisions about clinical trial enrollment and whether these benefits vary based on child demographic and psychosocial characteristics. In other words, do some children benefit more from involvement than others? For the purpose of this research, the potential benefits of assent include children's perceptions of the fairness of the decision making process and their sense of self-efficacy. The assumption of the proposed research is that how adults and children interact about the research decision is more relevant for children's self-efficacy than who ultimately makes the decision.

1.2 Relevant Literature and Data

For children to participate in research, both parental permission and child assent, defined as agreement to participate, must be obtained. The assent requirement can be waived if the research has the possibility of direct benefit to the child that can only be obtained in the research context, or if the child is judged incapable of assent. There has been much debate as to what constitutes assent and when children are capable of providing it. While the assent process is important for conforming to research regulations, it can also be used to enhance children's sense of self-efficacy. Self-efficacy is defined as confidence in one's ability to perform the actions needed to produce desired outcomes(1) and is important in predicting health-related behaviors and outcomes in children and adolescents with a chronic illness(2, 3). Self-efficacy may be particularly important in helping children to overcome barriers to successful illness management(4).

Prior research on child assent has been based primarily on a model that focuses on cognitive capabilities; this research examines children's understanding of research and the factors that influence their understanding(5-7). Research based on this model has found that rates of understanding of the various elements of research increase with age, and that children are more likely to understand some elements than others(8). Studies have also

compared children's competence to that of adults, with variable results depending on the age range of the sample and the methodology employed(8). A second model of child assent focuses on the relational context of children's decision making(9-11). This model recognizes that decision making typically occurs in a family context and attends to the role of collaborative decision making in normative development(12-14). The relational model reflects the view that children can be involved in decisions in various ways and that parents play an important role as sources of support and advice across the child's development. This approach to assent does not require that children meet some pre-specified criteria to be considered capable of assent, which may leave some children out of the process entirely(15). Instead, assent provides children with the opportunity to be involved in decision making, without necessarily having actual decision-making authority(16-19). For example, children can be provided with information about the decision or express an opinion about the decision to be made(16-19). This kind of involvement is hypothesized to teach children what factors others consider when making decisions, the consequences of different decisions, and the communication skills that are necessary to negotiate and influence decisions. In addition, children's involvement in decision making may enhance self-efficacy(12-14), facilitate open communication among clinicians, parents, and children, increase satisfaction with medical care and cooperation with treatment, and promote the ability to cope with illness(19-22). Optimizing children's roles in research decision making is critical, especially during pre-adolescence and adolescence, when children begin to strive for and acquire more decision-making independence.

The assumption of the proposed research is that how adults and children interact about the research decision is more relevant for children's sense of efficacy than who ultimately makes the decision. The focus is on parent-child interactions, because the family's typical pattern of decision making will shape how the decision about research is made, including the extent to which the child is involved in the decision(10, 23). Prior research related to the relational context of child assent, though limited and primarily qualitative, has found that the majority of children want parental input regarding research decisions or feel that the parent-child relationship plays an important role in these decisions(9, 10). Not surprisingly, there is variability in parent-child decision-making roles across families(11, 23), and roles also appear to depend on characteristics of the research, such as risk, benefit, and invasiveness(9, 11, 24-27).

In this research we will assess children's involvement in research decision making, within 10 days of families having made an actual decision about clinical trial enrollment for the treatment of a chronic condition in the child. To our knowledge, this will be the first study to assess the benefits of child assent, by measuring children's perceptions of the fairness of the decision-making process and self-efficacy (Aim 1). However, a relational approach to child assent is not "one-size-fits-all:" the optimal type or level of child involvement will depend on characteristics of the child, family, and situation(8, 15). For example, adolescents with high perceived stress or younger children may be overwhelmed by adults' attempts to solicit the child's opinion about a research trial. Or, children with a greater desire for decision-making involvement or prior research experience may feel disrespected or lacking in self-efficacy when only minimal involvement is sought from them. Such hypotheses have not been tested empirically and will be addressed in Aim 2. We will also test associations of child involvement with the perceived characteristics of the research, including risks, benefits, and research personnel behaviors (Aim 3).

This research will propel the field of child assent forward by conceptualizing assent not as a set of requirements that children must meet, but as a relational process by which children can participate in research decision making in multiple ways. Data from this research will help to determine the conditions under which varying levels of child involvement are more or less appropriate and has implications for ethical questions related to child assent, such as when and how children should be involved in research decision making. This research also will lead to the development of intervention strategies and guidelines to facilitate children's involvement in research decision making and enhance their sense of self-efficacy and control.

1.3 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

2.1 Primary Objective (or Aim)

The primary objective of this innovative research is to examine the benefits of children's involvement in decisions about clinical trial enrollment and whether these benefits vary based on child demographic and psychosocial characteristics.

Specific Aim 1: To determine the relationship between child involvement and the benefits of child assent

Specific Aim 2: To examine whether the relationship between child involvement and the benefits of child assent depends on child demographic and psychosocial characteristics (i.e., moderation)

Specific Aim 3: To determine the relationship between child involvement and research characteristics

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

This is an observational, cross-sectional study.

3.2 Study Duration, Enrollment and Number of Sites

Study duration is 2 years. We will enroll 190 parent-child dyads (180 evaluable). CHOP is the only site.

3.3 Total Number of Study Sites/Total Number of Subjects Projected

3.3.1 Duration of Study Participation

The participant's participation will last approximately 1 hour (30 minutes for parent; 30 minutes for child).

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at 1 investigative site in the United States (CHOP).

Recruitment will stop when approximately 190 dyads are enrolled. It is expected that approximately 190 dyads will be enrolled to produce 180 evaluable dyads.

3.4 Study Population

Participants will be children and parents who made a decision about whether to enroll the child in a Phase II, III, or IV clinical trial involving an intervention related to a chronic condition (e.g., cystic fibrosis, juvenile idiopathic arthritis, diabetes). Children with a cancer diagnosis will be excluded, due to the unique features of clinical research in this population. In two-parent families, both parents will be invited to participate, but participation by both parents will not be required.

3.4.1 Inclusion Criteria

- 1) Parents and children are English-speaking
- 2) Child between 10 and 17 years-old.

3.4.2 Exclusion Criteria

- 1) Child has no knowledge that a decision about clinical trial enrollment was made,
- 2) Child is unable to complete phone interview due to health status or functional impairment,
- 3) Child has a diagnosis of cancer,
- 4) Child has diagnosis of mental retardation or pervasive developmental disorder,
- 5) Child had psychiatric hospitalization in the past year.

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

4 STUDY PROCEDURES

4.1 Screening Visit

There will not be a screening visit. Review of eligibility will be conducted over the phone, after the parent has provided verbal consent.

4.2 Visit 1

There will be one visit, conducted over the phone, consisting of the following:

- Informed consent and parental permission
- Review of eligibility
- Child assent
- Verbal administration of questionnaires to child (see “Screening and Monitoring Evaluations and Measurements section”)
- Verbal administration of questionnaires to parent (see “Screening and Monitoring Evaluations and Measurements section”)

Parents and children will be interviewed separately and privately (i.e., out of earshot of the other member of the dyad).

4.3 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care.

4.3.1 Early Termination Study Visit

Subjects who withdraw from the study during the phone interview will not be given the \$20 gift card. If one member of the dyad completes the phone interview and the other does not, the individual who did complete the interview will receive a \$10 gift card.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Other Evaluations, Measures

- *Demographic Questionnaire*: Parents will complete a demographic questionnaire. Child data will include gender, age, race, ethnicity, birth order, chronic condition, date of diagnosis, perceived illness severity, and prior medical research participation. Parent/family data will include gender, age, race, ethnicity, highest educational grade, income, employment status, marital status, and number of children living in the home.
 - *Decision-Making Involvement*: Children and parents will complete the *Decision-Making Involvement Scale*. Support for the reliability and validity of the DMIS was reported in the Preliminary Studies section, and items were presented in Table 1. The questionnaire also has several filler items (e.g., We argued) to reduce the likelihood of socially desirable responding. Additional questions assess characteristics of the discussion and situation, including: satisfaction, importance, emotional tone, and extent of child symptoms during discussion. These items allow us to assess situation-specific influences on parent-child interactions. Specific items may be adapted to reflect the context of decisions about clinical trial enrollment.
 - *Fairness of Decision-Making Process*: We will assess the child's perception of the fairness of the decision-making process, with three items adapted from the empirical research related to the concept of procedural justice(28). If the Cronbach's alpha for these items is acceptable ($\geq .70$), ratings will be summed to obtain a total score; otherwise, items will be analyzed separately: (1) *Fairness*: How fair was the decision-making process about research participation? Children will respond on a 6-point Likert-type scale from "Very Fair" to "Not Fair At All." (2) *Satisfaction*: How satisfied are you with the decision-making process about research participation? Children will respond on a 6-point Likert-type scale from "Very Satisfied" to "Not Satisfied At All." (3) *Voice*: How much of a voice did you have in the decision-making process? Children will respond on a 6-point Likert-type scale from "A Lot of Voice" to "Not Much Voice At All."
 - *Self-Efficacy*: The *Decision Self-Efficacy Scale*(29, 30) assesses self-efficacy for making informed health-related decisions and will be completed by children. Items will be slightly adapted for use with children.
 - *Decision-Making Preference*: A single ordinal scale item will be adapted from Knopf and colleagues(31), to assess children's preference for involvement in medical decision making.
 - *Perceived Stress*: The 4-item version of the Perceived Stress Scale(32, 33) will be completed by children.
 - *Research Risk*: Children and parents will answer four questions about the perceived risks of the research: (1) "Do you think that you [your child] will experience any of the potential risks associated with the research?" (Risk Probability). Participants will respond on a 4-point scale: Definitely Yes, Probably Yes, Probably Not, and Definitely Not. Prior research suggests that the vast majority (84.2%) of 3rd graders (mean age 9 years) understand the distinction between "definitely" and "probably"(34). (2) How serious are the potential risks associated with this research study? (Risk Magnitude). Participants will respond on a 4-point scale: Not Very Serious, A Little Bit Serious, Quite Serious, Very Serious. (3) Do you think that other people will experience any of the potential risks of the
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research study? (Risk Other Probability) (4) How serious are these potential risks to others? (Risk Other Magnitude). Youth participants will be given the option of answering “Don’t Know” to these items (and the Benefit items below), because some children may be given little information about the research or may not understand the information they were given. If the Cronbach’s alpha for these items is acceptable ($\geq .70$), ratings will be summed to obtain a total score; if not, items will be analyzed separately.

- *Research Benefit*: Children and parents will answer six questions about the perceived benefits of the research study, with analogous response options as for perceived risk: (1) “Do you think that you [your child] will experience any of the potential health benefits associated with the research?” (Health Benefit Probability). (2) How important are these potential health benefits? (Health Benefit Magnitude). (3) Do you think that you [your child] will benefit in other ways by participating in this study? (Other Benefit Probability) (4) How important are these other potential benefits? (Other Benefit Magnitude). (5) Do you think that other people will experience any of the potential health benefits of the research study? (Health Benefit Others Probability) (6) How important are these potential benefits to others? (Health Benefit Others Magnitude). We will create subscale scores or analyze items separately depending on the Cronbach’s alphas for combinations of items (e.g., Benefit to Self; Benefit to Others).
 - *Solicitation of Child Involvement by Research Personnel*: The Decision-Making Involvement Scale will be adapted to assess child and parent perceptions of solicitation of child involvement by research personnel during the consent and assent process. For example, the item, “My mom/dad asked me for my opinion” will be adapted to “The researcher asked me for my opinion.” There is conceptual overlap between the behavior of parents and the behavior of research personnel with respect to seeking children’s involvement in research decision making: both can either facilitate or limit children’s involvement through their words and actions(35, 36). Adaptation of the items will be accomplished via team discussion and literature review. We do not expect the adaptations to be extensive.
 - *Additional Questions about the Decision*: Participants will answer the following questions: (1) Who made the final decision about the research study?” (Parent and child report). Response options will be: child alone, parent and child together, parent alone. (2) If it were totally up to you, would you have agreed or declined to participate in the research study? (Child report). We will also document if the family declined or consented to clinical trial enrollment.
 - *Functional Severity*: Parents will complete the short form of the Functional Status II-R(37), to account for the potential effects of functional impairment on children’s involvement in the research decision.
 - *Additional Data about the Clinical Trial*: For each participant, we will document which clinical trial they made a decision about and keep a copy of each clinical trial protocol. This will allow us to document additional features of the clinical trials that may be relevant to the analysis (e.g., trial phase; intervention type; duration of research; incentives; randomization; whether assent was required or waived).
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6 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

The primary endpoints are children's perceptions of the fairness of the decision making process and children's self-efficacy.

6.2 Control of Bias and Confounding

This is a cross-sectional, observational study, so subjects are not assigned by a process of randomization and are therefore subject to bias. As a convenience sample, our participants may differ in important ways from those who choose not to participate in the study, which will limit the generalizability of our findings. We will mention this as a limitation of our study in any publications.

6.3 Statistical Methods

6.3.1 Baseline Data

The primary and demographic variables will be examined with summary statistics, including means, medians, standard deviations (SD), minimum, and maximum values for continuous variables, and frequencies and proportions for categorical variables.

6.3.2 Analysis of Primary Outcome of Interest

Linear regression models will be used for examining the relationships among our primary variables. Demographic covariates will be entered into the models as appropriate. Only confounders with p-values < .10 will be retained for consideration in best-fitting, multiple covariate models. The selection of the pertinent regression model will be based on criteria for statistical significance of predictors which include Wald statistics, model R² values, partial R² values, and conditional error tests.

H1a: A single linear regression model will be tested, with Child Fairness score as the outcome of interest. The covariates of interest will be parent DMIS score and child DMIS score.

H1b: A single linear regression model will be tested, with Child Self-Efficacy score as the outcome of interest. The covariates of interest will be parent DMIS score and child DMIS score.

In Aim 2, we will assess the effect of moderation. Moderation occurs when the strength of the association between a predictor and dependent variable depends on a third variable, a moderator. Moderation is commonly assessed with multiple regression analysis by adding the interaction term between the independent variable and the moderator into the regression equation, which already include the intercepts and the independent variable.

H2a: Four linear regression models will be tested. The first two will include Child Fairness score as the outcome of interest and the second two will include Child Self-Efficacy score as the outcome of interest. The covariates of interest will be parent DMIS score, child DMIS score, the moderator of interest (either age or prior medical research experience), the

interaction of the moderator of interest with parent DMIS score, and the interaction of the moderator of interest with child DMIS score.

H2b: Four linear regression models will be tested. The first two will include Child Fairness score as the outcome of interest and the second two will include Child Self-Efficacy score as the outcome of interest. The covariates of interest will be parent DMIS score, child DMIS score, the moderator of interest (either decision-making preference or perceived stress), the interaction of the moderator of interest with parent DMIS score, and the interaction of the moderator of interest with child DMIS score.

H3a: Two linear regression models will be tested, the first with parent DMIS score as the outcome of interest and the second with child DMIS score as the outcome of interest. The covariates of interest will be risk probability and magnitude (parent and child report). Child age will also be entered as a covariate.

H3b: Two linear regression models will be tested, the first with parent DMIS score as the outcome of interest and the second with child DMIS score as the outcome of interest. The covariates of interest will be benefit probability and magnitude (parent and child report). Child age will also be entered as a covariate.

H3c: Two linear regression models will be tested, the first with parent DMIS score as the outcome of interest and the second with child DMIS score as the outcome of interest. The covariate of interest will be perceived solicitation of child involvement by research personnel (parent and child report). Child age will also be entered as a covariate.

6.4 Sample Size and Power

The sample size calculation is based on estimating prediction models describing the relationship between the DMIS and selected predictors using linear regression. For the multiple linear regression models, which include a maximum of four independent variables (for example, parent report of risk probability, parent report of risk magnitude, child report of risk probability, and child report of risk magnitude), with $R^2 = 20\%$, a sample size of 180 will have a power of 84% to detect at $\alpha = 0.036$ an increase in R^2 of 5% due to including two additional covariates such as child age and functional impairment. The desired sample size for this study is feasible at this site, given the large number of clinical trials being conducted at CHOP at a given time (about 350). A subset of these will be for the treatment of chronic conditions, but the numbers will still be large enough to ensure an adequate pool of potential participants.

7 SAFETY MANAGEMENT

7.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

7.2 Adverse Event Reporting

Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) these will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

8 STUDY ADMINISTRATION

8.1 Data Collection and Management

At the time of administration, the instruments will be coded with a number that is linked to the participant, so that once the study is complete, none of the research information can be linked back to any particular participant. Only research team members will have access to the raw data, to the statistical database, and to the database that links study ID numbers with participants' personal information. Birthdates will be collected from all child participants as this information is necessary to calculate exact age. After the completion of the entire study, the database that links ID Numbers to personal information will be destroyed.

All data collected for this research study will be obtained from identifiable human subjects for research purposes only. Birthdates and other Protected Health Information will be removed from the database and data collection materials at the end of the study. Mailing addresses will not be linked to research data and will only be linked to the participants' study ID number for sending gift cards. Mailing addresses will also be destroyed at the end of the study.

All data will be stored securely in locked storage cabinets in a locked research office, to be accessed only by members of the research team. All project data will be kept on a password-secure server which is backed up nightly. Access to the directory where the data will be stored will be restricted to the primary research team. Computer files will only contain study identifier codes and will be password-protected, with access limited to members of the research team.

Data collected as part of this study will be entered and stored using REDCap (Research Electronic Data Capture) database. REDCap is a secure web-based software solution and workflow methodology for supporting clinical and translational research databases. REDCap was developed by the informatics core at Vanderbilt University. Currently, many academic research communities, including CHOP, are part of the REDCap Consortium. REDCap provides data management functionality, including automated export procedures for seamless data downloads to Excel and commonly-used statistical packages (SPSS, SAS,

Stata, R). The database will incorporate range checks and between-variables consistency checks to ensure quality control. The system will signal the presence of questionable or potentially incorrect items. The database will be password-protected, stored, and backed up on a daily basis by CHOP's Research Institute. After data cleaning and quality assurance procedures are completed, pertinent sets of data will be converted into SAS or SPSS format for statistical analyses.

8.2 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy. The Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. In terms of confidentiality of the dyad, parents and children will be told at the beginning of each assessment that their responses are confidential and that they will not have access to each other's questionnaires. Families will also be assured that their responses to questionnaires will be kept confidential from members of the medical team. No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between provider (the PI) and any recipient researchers (including others at CHOP) before sharing a limited dataset (dates and zip codes).

8.3 Regulatory and Ethical Considerations

8.3.1 Data and Safety Monitoring Plan

In the unlikely event of a participant necessitating psychological treatment due to adverse effects of study participation, a member of the research team will make appropriate referrals within CHOP. Based on services available to families at CHOP, such a referral is likely to be effective in the event it is requested. Also, the investigator is experienced in talking with parents who are under the stress of a child's illness and with children in medical settings. The investigator will offer participants an opportunity to reflect on the experience (i.e., "debrief") after they have completed the instruments. Based on prior work, the investigator believes that most participants will find this experience thought-provoking and ultimately beneficial.

8.3.2 Risk Assessment

This is a minimal risk study. There are no physical risks associated with this study. Self-report assessments related to family decision making and other psychosocial issues may elicit temporary and mild negative feelings in some subjects; however, the likelihood of subjects experiencing prolonged or substantial distress is quite low. There is also the risk of a breach in confidentiality, if either the parent or the child overhears the other's phone interview. However, we will emphasize that each phone interview should be conducted in private so that the confidentiality of each participant's answers is maintained. Participation in this study requires that parents and children reflect on their decision to enroll in a clinical trial. As such, the study will be thought provoking, which we believe in most cases may be experienced as beneficial but could also lead to disturbing or second thoughts. There is the remote risk that a parent may reconsider the original decision to enroll his or her child in the

clinical trial. In this unlikely event, the parent will be referred back to the appropriate research team.

The psychological and emotional risks of this research will be dealt with through routine “debriefing” following the telephone interview. This will allow participants to reflect on their experiences. In the unlikely event of a participant necessitating psychological treatment due to adverse effects of study participation, a member of the research team will make appropriate referrals within CHOP. Based on services available to families at CHOP, such a referral is likely to be effective in the event it is requested. Also, the investigators are experienced in talking with parents who are under the stress of a child’s illness and with children in medical settings.

8.3.3 Potential Benefits of Study Participation

The research does not offer the prospect of direct medical or psychological benefit to the subjects, nor to others. There may be indirect benefits of reflecting on one’s own experience. As the risks of the research are appropriately characterized as “minimal risk”, they are reasonable in spite of the anticipated lack of direct medical or psychological benefit to subjects.

8.3.4 Risk-Benefit Assessment

The knowledge that may be gained from this research is of tremendous importance in understanding children’s involvement in decisions about clinical trial enrollment. Data from this project has implications for ethical questions related to child assent and will lead to the development of interventions and guidelines to enhance child involvement in research decision making. Again, as “minimal risk” research, the risks to subjects are reasonable with respect to the knowledge that may result from the research.

8.4 Recruitment Strategy

The team will identify eligible clinical trials through the IRB and the CTO at CHOP. After permission has been obtained from the Principal Investigator for each trial, the team will work with the Study Coordinator for each trial to identify potential participants. Families will be contacted by telephone after having made a decision to enroll in a clinical trial.

8.5 Informed Consent/Assent and HIPAA Authorization

If interested, the parent will be given a thorough explanation of the study, following a written script that includes all of the elements that are required for informed consent. These include the purpose, procedures, risks and benefits of participation, confidentiality, procedures for withdrawal, reimbursement, and contact information for study personnel. Families will be informed that their medical care at CHOP will not be affected if they choose not to participate in the proposed research. A waiver of written documentation of consent is requested, because recruitment, informed consent, and data collection will occur over the phone within 10 days of having made a decision to enroll in a clinical trial. This does not allow enough time to send and collect signed consent documents by mail. In addition, “the research presents no more than minimal risk of harm to subjects and involves

no procedures for which written consent is normally required outside of the research context” (45 CFR 46.117c2). After obtaining verbal informed consent and parental permission and HIPAA authorization from parents, we will review eligibility. If eligible, we will seek child assent. The assent process with children will include a developmentally-appropriate explanation of the purpose of the research, what research participation entails, and procedures for withdrawal from the study. Children will be informed that their participation is voluntary and that they can withdraw from the study at any time. Study personnel will then solicit the child’s willingness to participate in the research. Both the parent and child will be told that we can call back later or on another day if they need more time to make a decision. Completion of study questionnaires may occur during the initial phone call, or will be scheduled for another phone call within the 10 day window (from the day the family made a decision about clinical trial enrollment).

8.5.1 Waiver of HIPAA Authorization

We are requesting a partial waiver of HIPAA authorization, so that we can obtain verbal authorization. This is because recruitment, informed consent, and data collection will occur over the phone within 10 days of having made a decision to enroll in a clinical trial. This does not allow enough time to send and collect signed consent documents by mail. We confirm that the following criteria are met:

- (A) The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
 - (1) an adequate plan to protect the identifiers from improper use and disclosure;
 - (2) an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
 - (3) adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;
- (B) The research could not practicably be conducted without the waiver or alteration; and
- (C) The research could not practicably be conducted without access to and use of the protected health information.

8.6 Payment to Subjects/Families

8.6.1 Reimbursement for travel, parking and meals

None.

8.6.2 Payments to parent for time and inconvenience (i.e. compensation)

None.

8.6.3 Payments to subject for time, effort and inconvenience (i.e. compensation)

None.

8.6.4 Gifts

Each parent-child dyad that completes the questionnaires over the phone will receive a \$20 gift card to Amazon.com, Toys R' Us, or Target (their choice).

9 PUBLICATION

We will submit several manuscripts based on the study data to top-tier journals in pediatrics, bioethics, and pediatric psychology.

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APPENDIX

Questionnaires are uploaded in the Documents section of the eIRB protocol.
