Supporting Statement A for

Interactive Informed Consent for Pediatric Clinical Trials

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Table of contents

A. JUSTIFICATION....4

A.1 CIRCUMSTANCES MAKING THE COLLECTION OF INFORMATION NECESSARY....4

A.2. PURPOSE AND USE OF THE INFORMATION COLLECTION....2

A.3 USE OF INFORMATION TECHNOLOGY AND BURDEN REDUCTION....9

A.4 EFFORTS TO IDENTIFY DUPLICATION AND USE OF SIMILAR INFORMATION....11

A.5 IMPACT ON SMALL BUSINESSES OR OTHER SMALL ENTITIES....12

A.6 CONSEQUENCES OF COLLECTING THE INFORMATION LESS FREQUENTLY....12

A.7 SPECIAL CIRCUMSTANCES RELATING TO THE GUIDELINES OF 5 CFR 1320.5....12

A.8 COMMENTS IN RESPONSE TO THE FEDERAL REGISTER NOTICE AND EFFORTS TO CONSULT OUTSIDE AGENCY....12

A.9 EXPLANATION OF ANY PAYMENT OF GIFT TO RESPONDENTS....12

A.10 ASSURANCE OF CONFIDENTIALITY PROVIDED TO RESPONDENTS....13

A.11 JUSTIFICATION FOR SENSITIVE QUESTIONS....13

A.12 ESTIMATES OF HOUR BURDEN INCLUDING ANNUALIZED HOURLY COSTS....13

A.13 ESTIMATE OF OTHER TOTAL ANNUAL COST BURDEN TO RESPONDENTS OR RECORD KEEPERS....15

A.14 ANNUALIZED COST TO THE FEDERAL GOVERNMENT....16

A.15 EXPLANATION FOR PROGRAM CHANGES OR ADJUSTMENTS....16

A.16 PLANS FOR TABULATION AND PUBLICATION AND PROJECT TIME SCHEDULE....16

A.17 REASON(S) DISPLAY OF OMB EXPIRATION DATE IS INAPPROPRIATE....17

A.18 EXCEPTIONS TO CERTIFICATION FOR PAPERWORK REDUCTION ACT SUBMISSIONS....17

List of Attachments

Attachments

1a. Pre test

1b. Post test interview

1c. Post test

2. Perceptions Questionnaire

3. SORT-R3 Instrument

4. SNS Questionnaire

5. UM IRB-Med Approval Letter

6. Script Consent

A.1 Circumstances Making the Collection of Information Necessary

Informed consent is an essential component of recruitment in clinical trials. The informed consent process requires that patients and research subjects not only be given information about proposed medical treatments and research, but that it be presented in an understandable way so the individuals can make meaningful informed choices. Beauchamp and Childress describe three required elements of informed consent i.e., the threshold, information, and consent elements. Unfortunately, several studies suggest that the essence of the information element i.e., disclosure, recommendation of a plan, and understanding, is often not achieved due to poor disclosure and a lack of understanding of the material. If the patient or research subject does not achieve understanding, then the informed consent process by definition cannot take place. A significant effort has been placed on ensuring that sufficient information has been disclosed to achieve "informed" consent. However, disclosure alone does not ensure informed consent.

The informed consent process is intended to empower the patient to make a meaningful decision on clinical trial participation. Informed consent educates the patient on the risks, benefits, and alternatives to participation in a clinical trial, so that the patient can make a rational decision.

In recent years, a number of studies have questioned the quality of understanding achieved by the traditional informed consent process (typically in the context of informed consent for medical procedures). At the heart of the informed consent doctrine is the notion that the patient or research subject understands the procedure/therapy/study as well as its benefits and risks. Unfortunately, this is frequently not the case. Indeed, several studies suggest that many patients do not understand, recall, or even read the consent form.

In a study of 51 cataract surgery patients, only 18% could recall the risk factors immediately after their consent was obtained.[1] Furthermore, in a study of patients receiving blood transfusions, 88% could not recall the discussion of specific transfusion risks or alternatives to donor blood.[2] Barrett showed that half of a sample of oncology patients

involved in clinical trials failed to understand that clinical trial treatment was not equivalent to standard treatment and may involve additional risk when compared with standard treatment.[3]

Pediatric clinical trials may face even greater challenges. Research findings indicate there are differences in adolescent and parent understanding and appreciation of research risks and procedures, that opinions about decision-making authority and physician influence for research participation are different in adolescents and parents, and that financial compensation can be a salient factor in the research-related decision-making process. In fact, a study that compared pediatric and adult informed consent processes found that adult oncology decision makers were, on average, more fully informed and more actively engaged by their oncologists.[4] Research into the consent process has shown that central concepts in pediatric research such as randomization and the distinctions between phases of clinical trials are not uniformly understood by parents or older pediatric patients.[5] One study found that half of the parents did not understand randomization for childhood leukemia trials.[6] This problem may be exacerbated in some groups. Problems of consent-related communication and understanding are more frequent among parents of low social status who spoke little or no English.[7]Work by Tait et al. demonstrates that understanding of the protocol, study duration, risks, and direct benefits has significant room for improvement.[8]

A patient's lack of understanding undermines the central tenants of informed consent and poses serious ethical, legal, and practical issues. For instance, the ethical backbone of informed consent is compromised if patients fail to understand the experimental nature of the trial in which they are participating. Many patients make choices they regret based upon a limited understanding of the informed consent material. Clinical trial participants who do not believe they fully understand the implications of trial participation may ultimately feel regret about their decision to participate.[9] A study of pediatric clinical trials identified several predictors of consent including: the degree to which the parent read the consent document, the characteristics of the consent document, parental understanding, the perceived importance of the study, and perceived benefits.[10]

A.2 Purpose and Use of the Information Collection

Given that the standard verbal and/or written methods of communicating medical information are often inadequate, several alternative strategies have been explored with mixed success. Such strategies include the use of modified consent forms with improved readability and processability (formatting), inclusion of graphics, extended discussions, teaching aids, and video technology (including colonoscopy, knee arthroscopy, hormone replacement therapy, and the use of intravenous contrast media).[11, 12, 13] Of these, video presentations have shown the most promise in improving patients' knowledge of treatments and procedures. However, the effectiveness of video presentations is limited by their passive and often generalized nature. Expanding upon this learning paradigm, new developments in interactive computer-based technologies offer the potential to overcome these limitations. Engaging and adaptable exercises can promote active learning and offer a highly customized informed consent process that addresses a patient's specific needs and level of understanding. Interactive computer-based technologies can overcome traditional limitations by promoting active participation in learning and allowing subjects to access information that is consistent with their learning styles and health literacy.

The disclosure of the risks and benefits of a clinical trial is perhaps the most important determinant of a subject's consent to participate. Yet, despite this, there is a paucity of data that address the presentation of these elements to patients. Although a few studies have examined different strategies for explaining risks and benefits of treatment decisions or diagnoses, these have often focused on the presentation of single risk rather than comparative risk statistics, and are not in the context of a clinical trial. There appears to be no consensus regarding the optimal method of framing comparative risk/benefit information. Relative risk is sometimes used as a means to provide information on the magnitude of a change in risk, however, it does not provide a reference by which to place that change in context. Recently, Zikmund-Fisher et al. showed that women who viewed an incremental risk presentation regarding the use of tamoxifen for breast cancer reported significantly less worry and greater understanding about the risk compared to women who were given absolute risk information.[14] These authors suggest that this may

occur because incremental risk helps focus attention on the actual change in risk by providing information regarding both the baseline risk and the change.

Patients understanding of the potential risks and benefits associated with a study, as well as their rights as research participants is crucial to ethical clinical research informed consent for procedures are also present when applied to clinical trials.

The nature of clinical trials imposes unique demands upon informed consent. It is important to neither create false hopes nor a sense of futility. In practice, studies demonstrate a significant need to improve informed consent for clinical trials. Therapeutic misconception (the belief that investigation is an extension of treatment and that it is especially likely to be effective) is widespread. Lack of understanding about randomization has also been documented.

We hypothesize that use of the Interactive Informed Consent Program for Pediatric Clinical Trials by parents and youth will increase knowledge about the clinical trials, study procedures and informed consent. This research will allow for a better understanding of the best methods for consenting individuals for medical procedures. It will additionally contribute to the foundation of a best practices approach to informed consent.

An evaluation team at the University of Michigan (contracted by ArchieMD, and have no involvement in product development) will evaluate the efficacy of the informed consent module. This team is an impartial group that will ensure that data collected is unbiased.

On the commercialization side, representatives of the developer have contacted Elsevier Science, a global health science publisher that has recently contracted to license existing visual technology as well as perform developmental work. As an extension of this relationship, business discussions with the 6-12 division of Harcourt are in-process, (a Reed-Elsevier company), regarding the publishing and distribution of an expanded product that would include additional content in the form of other drugs and some enhancement of the interactivity. A publishing and distribution partnership with a company of this size and scope would enable wide distribution of the product. Results from this evaluation may be used for marketing purposes if the evaluation suggests an increase in knowledge. If the evaluation results suggest

that there is no benefit to this learning mode, it is anticipated that this will not be used for marketing purposes, but will still be written up for a peer reviewed publication submission

References

1. Vallance, J., M. Ahmed, and B. Dhillon, Cataract surgery and consent; recall, anxiety, and attitude toward trainee surgeons preoperatively and postoperatively. J Cataract Refract Surg, 2004. **30**(7): p. 1479-1485.2. Chan, T., et al., Consenting to blood: what do patients remember? Transfus Med, 2005.**15**(6): p. 461-466.

3. Barrett, R., Quality of informed consent: measuring understanding among participants in oncology clinical trials. Oncol Nurs Forum, 2005. **32**(4): p. 751-755.

4. Simon, C.M., et al., Comparison of the informed consent process for randomized clinical trials in pediatric and adult oncology. J Clin Oncol, 2004. **22**(13): p. 2708-17.

5. Barfield, R.C. and C. Church, Informed consent in pediatric clinical trials. Curr Opin Pediatr, 2005. **17**(1): p. 20-4.

6. Kodish, E., et al., Communication of randomization in childhood leukemia trials. JAMA, 2004. **291**(4): p. 470-5.

7. Simon, C., et al., Groups potentially at risk for making poorly informed decisions about entry into clinical trials for childhood cancer. J Clin Oncol, 2003. **21**(11): p. 2173-

8. Tait, A.R., et al., Improving the readability and processability of a pediatric informed consent document: effects on parents' understanding. Arch Pediatr Adolesc Med, 2005. **159**(4): p. 347-52.

9. Stryker, J., et al., Understanding the decisions of cancer clinical trial participants to enter research studies: Factors associated with informed consent, patient satisfaction, and decisional regret. Patient Educ Couns, 2005.

10. Tait, A., T. Voepel-Lewis, and S. Malviya, Participation of children in clinical research: factors that influence a parent's decision to consent. Anesthesiology, 2003. **99**(4): p. 819-825.

11. Rossi, M., et al., Video informed consent improves knee arthroscopy patient comprehension. Arthroscopy, 2005. **21**: p. 739-743.

12. Rostom, A., et al., A randomized trial of a computerized versus and audio-booklet decision aid for women considering post-menopausal hormone replacement therapy. Patient Educ and Counsel, 2002. **46**: p. 67-74.
13. Hopper, K., et al., Interactive method of informing patients of the risks of intravenous contrast media. Radiology, 1994. **192**: p. 67-71.
14. Zikmund-Fisher, B., et al., Alternate methods of framing information about medication side effects: Incremental risk versus total risk difference. J Hlth Comm, 2008. **13**: p. 107-124.

A.3 Use of Information Technology and Burden Reduction

While the method of product delivery and assessment itself involve technological aspects, the information collection will be executed through paper and pen and technology, as follows:.

1) a pre-test interview to determine understanding of clinical trial concepts (4 items): Participants' responses to paper data collection instrument questions, Appendix A: "Clinical trial concepts Pre-test (baseline) interview," will be written down verbatim by trained interviewers and then manually entered into an anonymous database (no-identifiers) by trained research nurses and research assistants from the University of Michigan's Department of Anesthesiology. Data entry will be checked and double-checked by different research nurses and assistants.

2) a post-test interview (following administration of either the standard written consent information or the ArchieMD program) to determine participants' "new" understanding of clinical trial concepts (4 items): This is #9 of Appendix A, "Post-test Interview" (see #3, immediately below).

3) a post-test interview to determine understanding of details of the clinical asthma trial (12 items): Participants' responses to paper data collection instrument questions, Appendix A: "Post-test interview," will be written down verbatim by trained interviewers and then manually entered into an anonymous database (no-identifiers) by trained research nurses and research assistants from the University of Michigan's Department of Anesthesiology. Data entry will be checked and double-checked by different research nurses and assistants.

4) A questionnaire to determine perceptions of the information provided (9 items): Participants' responses to paper data collection instrument questions, Appendix B: "Perceptions Questionnaire," will be written down verbatim by trained interviewers and then manually entered into an anonymous database (no-identifiers) by trained research nurses and research assistants from the University of Michigan's Department of Anesthesiology. Data entry will be checked and double-checked by different research nurses and assistants.

5) the SORT-R3 instrument for determining literacy (number of items varies): This will be completed by trained interviewers. The answers will be manually entered into an anonymous database (no-identifiers) by trained research nurses and research assistants from the University of Michigan's Department of Anesthesiology. Data entry will be checked and double-checked by different research nurses and assistants.

6) the SNS instrument for determining numeracy (8 items): Participants' parents will complete this instrument via paper and pen. The answers will be manually entered into an anonymous database (no-identifiers) by trained research nurses and research assistants from the University of Michigan's Department of Anesthesiology. Data entry will be checked and double-checked by different research nurses and assistants.

The privacy act does apply to this submission as determined by the NIH Privacy Act Officer. The data collection is covered by NIH Privacy Act Systems of Record 09-25-0156, "Records of Participants in Programs and Respondents in Surveys Used to Evaluate Programs of the Public Health Service, HHS/PHS/NIH/OD". A Privacy Impact Assessment will be conducted once the study obtains clearance and annually thereafter as required.

A.4 Efforts to Identify Duplication and Use of Similar Information

To our knowledge, this will be the first project to utilize an interactive computer based informed consent module to educate parents, guardians, and children regarding research participation.

A.5 Impact on Small Businesses or Other Small Entities

No small businesses or other small entities will be involved in this study.

A.6 Consequences of Collecting the Information Less Frequently

A data collection schedule has been developed that minimizes the number of times that data needs to be collected. Data will be collected at 2 points (pre-test, post-test). If data were to be collected less frequently, it would not be possible to measure any changes in knowledge and attitudes.

A.7 Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

This information collection fully complies with all guidelines of 5 CFR 1320.5.

A.8 Comments in Response to the Federal Register Notice and Efforts to Consult

The 60 day FRN was published on 05/9/2013 (Vol. 78, No. 90, page 27243). No comments were received.

A.9 Explanation of Any Payment of Gift to Respondents

The evaluation of the ArchieMD Pediatric Informed Consent Program for Clinical Trials will take approximately 30-40 minutes to complete. Parents and children will be interviewed, as described, to elicit their understanding of key clinical trial concepts (randomization, blinding, etc.) and their understanding of details of the clinical asthma trial presented using either standard written consent information or the ArchieMD interactive program. For their time and contribution, and potential inconvenience, parents and children will each receive a one-time $10 gift card. This amount is consistent with previous studies that we have employed using similar methodology and the same populations. This payment amount has been approved by the University of Michigan's Institutional Review Board.

A.10 Assurance of Confidentiality Provided to Respondents

Given that this research involves human subjects all matters related to the protection of human subjects under the Code of Federal Regulation (45CFR 46 and 45 CFR 46 Subpart D for children) will be adhered to.

Data to be collected will be obtained using semi-structured interviews as described previously. We will not review any personal medical information for enrollees nor will any of the interview questions contain any sensitive information. We will record subject age, sex, and race (principally for NIH reporting purposes). We anticipate that the time taken for all study aspects will be 30-40 minutes. The risks of this study are no more than minimal and are primarily ones of privacy. However, to protect the privacy of the participants, responses from the pre- and post-test interviews and the assessment tools (literacy and numeracy tests) will be

linked by a code number only. Once the pre and post-tests are collected, all identifiers will be destroyed. None of the data collection sheets will contain any identifiers and the database will be totally anonymous. Parents and children will not be tested or contacted at a later date. All data will be presented in aggregate form only. No individuals can be identified.

A.11 Justification for Sensitive Questions

There are no sensitive questions. No protected health information (PHI) or other personal identifiable information (PII) will be collected. All data collection sheets and the final database will be anonymous.

A.12 Estimates of Hour Burden Including Annualized Hourly Costs

The estimated number of respondents is 284 (136 children and 148 parents). Each participant will complete 1) a pre-test interview to determine understanding of clinical trial concepts (4 items), 2) a post-test interview (following administration of either the standard written consent information or the ArchieMD program) to determine participants' "new" understanding of clinical trial concepts (4 items), 3) a post-test interview to determine understanding of details of the clinical asthma trial (12 items), 4) A questionnaire to determine perceptions of the information provided (9 items), 5) the SORT-R3 instrument for determining literacy (number of items varies), 6) the SNS instrument for determining numeracy (8 items), and 6). Based on our experience with these interviews and tests, we anticipate that the process will take 30-45 minutes (0.5-0.72 hour burden/participant; average 0.61). All participants will complete these study tests ONCE only. There is no hourly rate paid to the participants since the hourly burden is not expected to vary. All participants will receive a one-time $10 gift card for their time. The annualized cost per participant will be $10 or $284 for the entire population.

A.12-1 Estimates of Hour Burden

Type of Respondents	Survey Instrument	Number of Respondents	Number of Responses Per Respondent	Average Time per Response (in hours)	Total Burden Hours
Children	Script consent	136	1	1/60	2
	Pre-test interview	136	1	3/60	7
	Post-test 1C interview	136	1	3/60	7
	Post-test 1B interview	136	1	12/60	27
	Perceptions of the program	136	1	9/60	20
	SORT-R3 for literacy	136	1	5/60	11
	SNS for numeracy	136	1	4/60	9
	Total			37/60	83
Parents	Script consent	148	1	1/60	2
	Pre-test interview	148	1	3/60	7
	Post-test 1C interview	148	1	3/60	7
	Post-test 1B interview	148	1	12/60	30
	Perceptions of the program	148	1	9/60	22
	SORT-R3 for literacy	148	1	5/60	12
	SNS for numeracy	148	1	4/60	10
	Total			37/60	90

A.12-2 Annualized cost to Respondents

Form Name	Type of Respondent	Number of Respondents	Total Annual Burden Hours	Hourly Wage Rate	Total Annual Cost
Consent (Attachment 6)	Children	136	2	$22.01	$44.02
	Parents	148	2	$22.01	$44.02
Pre Test interview (Attachments 1a)	Children	136	7	$22.01	$154.07
	Parents	148	7	$22.01	$154.07
Post Test interview (Attachments 1b and 1c)	Children	136	34	$22.01	$748.34
	Parents	148	34	$22.01	$748.34
Perceptions, SORT, SNS (Attachment 2,3,4)	Parents	148	45	$22.01	$990.45
	Children	136	45	$22.01	$990.45
				Total	$3,873.76

A.13 Estimate of Other Total Annual Cost Burden to Respondents or Record Keepers

No capital, start-up or operational and maintenance costs are incurred by study participants in this information collection activity.

A.14 Annualized Cost to the Federal Government

Total costs associated with the project are estimated to be approximately $70,000 over a 1 year contract performance period. These costs cover all aspects of survey design, testing, computer equipment, data collection and analysis and report generation. In addition, it is estimated that one full time equivalent NIDA staff member will spend 2 % of his/her time (40 hours) to manage and administer the project. Assuming an annual salary of $100,000, government personnel costs will be $2,000 over a 1 year period. The annualized project costs to the federal government is $72,000.

A.15 Explanation for Program Changes or Adjustments

This is a new information collection request.

A.16 Plans for Tabulation and Publication and Project Time Schedule

A.16 - 1 Project Time Schedule

Activity	Time Schedule
Recruitment and coordination of science classrooms	1 month after OMB approval
Send home informational memo	1-2 months after OMB approval
Administer pre-test	2 months after OMB approval
Intervention	2-3 months after OMB approval (1-2 weeks after pre-test)
Post Test	3 months after OMB approval (1-2 weeks after

	intervention)
Second Post test	9 Months after OMB approval (6 months after initial post test)
Analysis	10 Months after OMB approval
Final report	11 Months after OMB approval

A.17 Reason(s) Display of OMB Expiration Date is Inappropriate

The OMB expiration date will be displayed on all documents.

A.18 Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the "Exceptions to Certification for Paperwork Reduction Act Submissions."