Demographic, Clinical and Informed Consent Environment Factors that Influence Parents' Decisions to Enroll their Child in a Clinical Research Study

by

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ABSTRACT

Little research has been done on factors that influence parents' decisions to have their child participate in research studies. This information would allow investigators to better estimate participation for clinical trials and optimize the consent process to obtain parents' consent for research. This project is a retrospective analysis of demographic, clinical and informed consent environment factors of patients' whose parents were approached to have their child enrolled in a cardiology clinical study at the University of Michigan. The race, age, gender, clinical diagnosis, location of informed consent and title of consenter were analyzed for 351 patients. The results showed that only the consenter individual had a significant impact on whether parents consented to the study. Further research is necessary to confirm that the title of the informed consenter, not a specific individual, is a risk factor for successful consenting before the results can be generalized to other therapeutic areas.

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Chapter 1: Introduction

Problem Statement

With an ever-increasing volume of clinical trials being conducted worldwide, there exists great potential for improvement in clinical care, treatment and prevention of diseases that affect infants and toddlers. This potential could never have been discovered if it not had been for parents that were willing to enroll their children in research studies aiming to benefit the general knowledge of the clinical field. Investigators have explored parents' attitudes and understanding of research trials as factors that may influence decisions about enrolling their children in studies. However, little information is available specifically relevant to factors that may influence parents' decisions to allow their children to participate in clinical research. It is unknown whether circumstances surrounding the patients' demographics, clinical diagnosis and informed consent processes may have an influence on consent rates for these important trials. This project will investigate any associations between these previously unexamined factors and parents' willingness to have their child participate in a clinical research study.

Background

Clinical investigators have analyzed parents' attitudes towards certain research studies in which their children were eligible to participate in, specifically examining how parents react to certain features of the study being presented to them (Tait, Voepel-Lewis, Siewert, & Malviya, 1998). Furthermore, studies have been performed to investigate parents' analyses and understanding of research studies when approached by a physician versus other members of the clinical research team (Tait, Voepel-Lewis, & Malviya, 2004). In addition, associations between a child's health status at the time of informed consent and how their

parents would feel enrolling them in a study have been explored (Caldwell, Butow, & Craig, 2003). Although these analyses provided a good amount of knowledge to the field of clinical research, this project will specifically examine demographic, clinical, and informed consent environment factors and their influence on successful consenting with the primary outcome being whether or not a parent consented to have their child participate in a research study. The parents' understanding of the study or attitudes towards clinical research in general will not be considered.

Purpose and Objective

The primary objective of this project is to determine what demographic, clinical and informed consent process factors influence parents' decisions regarding whether or not to enroll their child into a clinical trial. Specifically, this project will investigate whether the patients' race, gender, age, severity and time of their clinical diagnosis, gestational age, presence of any chromosomal anomalies, location of informed consent and/or title of the healthcare professional administering the informed consent could have any effect on whether or not parents decide to have their child participate in a research study. By analyzing the influence that these factors may or may not have on rates of informed consent, we may be better able to predict future enrollment frequency for certain types of studies. Furthermore, investigators could adjust their informed consent processes by knowing which environmental factors lead to a higher participation rate for their clinical trials.

Justification and Significance

Finding an association between demographic, clinical and consent environment factors and the decision to participate in a clinical trial would allow investigators and research study staff to better estimate enrollment rates as well as the ability to optimize the

informed consent process in a way that favors a higher participation frequency. Few studies have examined factors or outcomes of the informed consent process with regard to parents' allowing their children to participate in research (Franck, Winter and Oulton, 2006). Having more information about parents' attitudes and willingness to participate in medical research involving their children will permit researchers to enhance the way in which informed consent is sought for clinical studies (Langley, Halperin, Mills, & Eastwood, 1998). Several studies have examined parents' sociodemographic status and risk-benefit analysis of the study and whether those points influence consent rates for pediatric trials (Harth & Thong, 1990; Tait et al., 2004). This project will support and extend the knowledge gained by these investigations by analyzing, in addition to demographic factors, the effect of a child's clinical diagnosis and its severity as well as the informed consent environment (including the title of the healthcare professional obtaining consent) on parents' decisions to consent to or decline their child's participation in clinical research. The ability to better predict enrollment rates and participation in clinical trials may ultimately prove beneficial to the field of clinical research, as it will facilitate a more efficient study enrollment process.

Research Questions and Hypotheses

Based on previous research performed on the topic, I predict that white parents will be more likely to allow their child to participate in research than minority parents (Shavers, Lynch, & Burmeister, 2002). I also predict that parents with older children (ages one year and older) will have a higher rate of consent than parents with children who are under one year of age based on my experience as a clinical research coordinator. Furthermore, I hypothesize that children with less severe clinical diagnoses (both

physical and chromosomal) will have a higher participation rate than those children with more severe diagnoses (Caldwell et al., 2003)

Based on my experience with approaching parents for their child's participation in neonatal and pediatric studies, I also hypothesize that parents' whose children have been clinically diagnosed prenatally will be more inclined to enroll their child in a clinical study as compared with parents whose children were diagnosed after birth. Furthermore, I predict that parents whose children have had more surgical experience than those who have not will be more likely to consent to a clinical trial.

In terms of the informed consent environment, I predict that parents who were approached for informed consent in an outpatient setting (such as a doctor's office or clinic) will be more likely to have their child participate in research than parents who were approached in an inpatient hospital setting (Burgess, Singhal, Amin, McMillan, & Devrome, 2003). In general, I hypothesize that patients who were approached for consent by a physician will have a higher rate of participation than parents who were approached by a research nurse, who will in turn have a higher enrollment rate than a clinical research coordinator (Maltby, 1993).

Chapter 2: Review of Literature

Previous literature has shown an interest in investigating parents' attitudes towards enrolling their children into clinical research studies, specifically taking a look at aspects of studies themselves as having influence on parents' decisions to consent. A study performed at the University of Michigan consisted of administering a survey to parents who were approached to have their child participate in an anesthesia clinical trial (Tait et al., 1998). The survey contained items inquiring about the importance of factors used in the families' decision process at the time of informed consent. The results demonstrated that the significant factors that "non-consenting" parents considered while deciding whether to have their child participate in research are the fear of the unknown, fear of lack of safety of their child, fear of potential risk to their child and fear of randomization within the study itself (Tait et al., 1998). Parents who did consent to have their child participate in the study were found to have felt that their participation would contribute to medical science, that other children would benefit from their decision, that the study was important and explained well by the consenter, and that the study was of minimal risk to their child. It is also important to note from this investigation that a significant difference existed between "consenters" and "non-consenters" in that consenters were more likely to enroll their child into a study if the child had previously participated in a clinical trial as compared with parents whose children had not participated in a study previously.

Burgess et al. (2003) performed a study to better help the understanding of parental perceptions of the informed consent process for clinical trials. The investigators developed and administered a questionnaire to parents who had agreed to have their child participate in a research study while their infant was a patient in the

Neonatal Intensive Care Unit (NICU). Over half of consenting parents felt that they had enough time to ask questions about the study and were given a chance to discuss enrollment of their child with supportive family members. A large majority of these parents reported that they understood their right to decline participation in the study. Although previous research has suggested that obtaining informed consent in an intensive care unit may be coercive (Maltby, 1993), only approximately one-third of parents felt pressured and/or obligated to have their baby participate in the NICU studies (Burgess et al., 2003). In support of obtaining informed consent in inpatient settings, Troung, Weeks, Cook & Joffe (2011) reported that parents who were approached about research studies that their children were eligible for were more likely to enroll their child in that study if the informed consent took place while the child was a patient in the hospital. Furthermore, these parents were more likely to have retained information and have a greater understanding of the clinical trial if the informed consent process was completed in an inpatient setting.

It has been suggested that obtaining informed consent from parents by a physician could result in better enrollment and retention rates; however, one may consider consent being obtained by a physician could be considered coercive (Maltby, 1993). This was explored further in a study that examined factors that influenced parents' understanding of the risks and benefits of surgical research trials in which their children could participate (Tait et al., 2004). Parents who both consented and declined their child's participation again completed questionnaires containing items measuring their understanding of the trial that was presented to them. Parents whose children were enrolled in a previous study were more likely to assess the risk/benefit as more positive than those with no research experience. Furthermore, parents who were consented by a physician were more likely to rate the direct

benefits as more beneficial to their child than if they were approached for consent by a non-physician member of the research team (Tait et al., 2004). There was no difference in risk/benefit analysis and understanding between parents who approached for consent the day before their child's surgery or the day of the surgery.

Another potentially influential factor that has been explored in terms of parents enrolling their children in clinical research is the health status of the child at the time of informed consent approach. According to Caldwell et al. (2003, p. 557), parents thought that "those who had a child with a life-threatening condition would be more prepared to participate in trials, in the hope of finding the 'miracle cure'". Furthermore, parents acknowledged that perhaps those with healthy children might underestimate minimal illnesses and view participation in research as unnecessary. These investigators reported that a large amount of parents confessed that the severity of their child's illness came into effect while they made a decision about participating in a clinical study.

Chapter 3: Research Design and Methodology

This study is a retrospective review of quantitative secondary data from a pediatric clinical trial currently being performed at C.S. Mott Children's Hospital at the University of Michigan in Ann Arbor. I received approval for this project through the University of Michigan Institutional Review Board as well as the Eastern Michigan University Human Subjects Review Committee.

Patient Population

The population that was analyzed consists of 351 patients less than three years of age whose parents were approached to have their child participate in a therapeutic pediatric cardio-thoracic intensive care unit trial that potentially involves minor increase over minimal risk to its participants. Patients were included in the analysis regardless of whether the parents consented to or declined the study. These parents were approached for their child's participation in the trial beginning at the start of the study in April 2008 and although the trial remains currently enrolling, the population being studied for this particular project consists of patients' parents approached through May 2011.

Data Collection and Methods of Analysis

The data was gathered by compiling demographic, clinical and consent process information collected through normal screening and data collection procedures for the study into a SAS (Statistical Analysis System, SAS Institute Inc.) database. The data was collected from the clinical trial's screening, eligibility and enrollment logs. Specifically, the data collected from each patient consisted of their race, age at the time their parents were approached about the clinical trial, gender, clinical diagnoses, severity of their diagnoses, gestational age at time of birth, number of previous surgeries (if any), whether the patient

was diagnosed with their congenital heart defect before or after birth, the location of approach for consent, the title of the healthcare professional (consenter) who approached the family about the study, and whether or not the parent consented to their child's participation in research. The patients' Risk Adjustment for Congenital Heart Surgery (RACHS) scores were also collected. RACHS scores are uniformly used to determine severity and risk of cardiac surgery patients' congenital heart defects and are determined by the patients' physician (Jenkins, 2004). Any qualitative variable (such as race, clinical diagnosis, consent location and consenter title) was coded and given a numerical value in order to facilitate analysis. The dataset was completely de-identified according to HIPAA compliance with no potential for patients to be re-identified. No contact was made with the patients included in the study population, and because the study is a retrospective data review, the study is of less than minimal risk to the involved patients.

Chi squared tests were administered to the data in order to determine any significant associations between certain groups of patients and their participation in the research trial. Furthermore, any factor with a significant association will be analyzed using logistical regression to determine if any statistically significant influences exist on successful consenting.

Definition of Terms

For the purposes of this project and because of the demographics of the study population, patients' races are defined as either "white" or "other". Patients fell into one of three categories according to their age: neonate (0-29 days), infant (30 – 365 days) and toddler (>365 days). Their congenital heart defect diagnoses were categorized into one of

twelve categories: 1 = Situs Defects, 2 = Atrial Septal Defects, 3 = Ventricular Septal Defects, 4 = Endocardial Cushion Defects, 5 = Single Ventricle Defects, 6 = Great Vessel/Aortic Arch Defects, 7 = Coronary Artery Anomalies, 8 = Left Heart Lesions, 9 = Right Heart Lesions, 10 = Cardiomyopathy, 11 = Electrophysiological Defects, and 12 = Miscellaneous Defects. These categories were pre-determined by the pediatric cardio-thoracic intensive care unit trial study protocol and were adapted for use for this project. The patients' RACHS-1 scores on a scale from 1 to 6 (1 being the least severe and 6 being the most severe) categorized the severity and risk of these congenital heart defects (Jenkins, 2004). The location of the consent process consisted of four areas: an outpatient pre-operative clinic and the inpatient areas including the general care floor, the pediatric cardio-thoracic intensive care unit and the neonatal intensive care unit at C.S. Mott's Children's Hospital at the University of Michigan in Ann Arbor.

Chapter 4: Presentation and Analysis of Data and Results

Description of the Population

Three hundred and fifty-one patients were included in the analysis, with 256 patients' whose parents consented to the study (consenters) and 96 patients whose parents declined their child's participation in the trial (non-consenters). Table 1 describes the demographic factors of the patients included in the analysis.

Table 1

Description of Patients' Demographic Factors

	N	%
Age at time of informed consent (in days)[1]		
<30	93	27
30-364	183	52
>365	75	21
Gender		
Male	193	55
Female	158	45
Race		
White	275	78
Other[2]	76	22

Note. [1]Patients' median (IQR) age at time of informed consent was 129 (IQR) days. [2]Patients who were of African American, Middle-eastern, Hispanic and Bi-racial descent were grouped together in the 'other' category.

A majority (52%) of patients were between 30 and 364 days old, while 27% of patients were less than 30 days old and 21% of patients were over the age of one year. The patients' median (IQR) age was 129 (IQR) days. More than half (55%) of patients were males. As consistent with the patient population seen at the University of Michigan, a large majority of patients (78%) were White.

In terms of the clinical information for the patient population, Table 2 shows the distribution of the patients' clinical diagnoses.

Table 2

Description of Patients' Clinical Diagnoses

	N	%
Prenatal diagnosis of CHD		
Yes	165	47
No	185	53
Unknown	1	<1
Presence of chromosomal anomaly		
Yes	61	17
No	290	83
Premature birth[1]		
Yes	49	14
No	302	86
Type of heart defect		

Situs defects	2	1
Atrial septal defects	24	7
Ventricular septal defects	64	18
Endocardial cushion defects	30	9
Single ventricle defects	84	24
Great vessel/aortic arch defects	71	20
Coronary artery anomalies	2	1
Left heart lesions	15	4
Right heart lesions	55	16
Cardiomyopathy	1	<1
Miscellaneous	3	1
RACHS-1 Score		
1	16	5
2	141	40
3	106	30
4	54	14
5	1	<1
6	29	8
N/A[2]	4	1
Number of previous surgeries		
0	246	70
1	59	17

2	35	10
≥ 3	12	3

Notes. [1]For this data, premature birth is defined as having a gestational age of <37 weeks. [2]These patients were not eligible to receive a RACHS-1 score at the time of their procedure.

One hundred sixty-five patients (47%) had a pre-natal diagnosis of their congenital heart defect. A majority of our patients (83%) did not have a chromosomal anomaly, and only 49 (14%) were birthed prematurely.

The most common type of congenital heart defect is a single ventricle defect, as 84 (24%) of the patients were diagnosed with this kind of disease. The other more common types of defects were defects of the great vessels and aortic arch, ventricular septal defects and right heart lesions. This is consistent with the patient population that is seen at the University of Michigan. A total of 75% of the patient population had a RACHS score between 1-3, indicating that their congenital heart defect surgery was less risky than the other patients involved in the analysis. Eighty-four patients (24%) had a RACHS score of 4-6, indicating a more severe and risky diagnosis. A large majority of patients (70%) had no previous heart surgeries prior to their parents being approached for research, and only 3% of patients had endured more than three surgeries.

Lastly, Table 3 describes the patients' informed consent environment at the time that their parents were approached regarding the research study.

Table 3

Description of Patients' Informed Consent Environment

	N	%
Location of informed consent		
Outpatient Clinic	232	66
Inpatient non-ICU floor	24	7
Pediatric Cardio-Thoracic ICU	46	13
Neonatal ICU	49	14
Title of consenter		
Clinical research coordinator	151	43
Clinical research nurse	117	33
Physician (MD)	83	24

A majority of the parents (66%) were approached for informed consent in the outpatient clinic, while only 34% of parents were described the study in the inpatient areas (non-ICU, PCT-ICU, and NICU). Furthermore, 151 patients' parents (43%) were approached for consent by the study's clinical research coordinator, 117 (33%) were approached by the clinical research nurse, and 83 (24%) of parents were approached by the study physician. The three individuals who approached parents for consent remained consistent throughout the entire study. It should be noted that the clinical research coordinator in this study is myself.

Univariate Analysis

A univariate analysis was performed in order to determine the existence of relationships between each single variable and the outcome of a successful informed consent (Table 4).

Table 4

Associations Between Demographic, Clinical and Informed Consent Environment Factors and Successful Consenting

	Consented N (%)	p
Age at time of informed consent (in days)		.687
<30	71 (76)	
30-364	131 (72)	
>365	54 (72)	
Gender		.132
Male	147 (76)	
Female	109 (69)	
Race		.365
White	204 (74)	
African American	22 (63)	
Other	30 (73)	
Prenatal diagnosis of CHD		.209
Yes	115 (70)	
No	140 (76)	

Presence of chromosomal anomaly		.430
Yes	42 (69)	
No	214 (74)	
Premature birth		.928
Yes	36 (73)	
No	220 (73)	
RACHS-1 Score[1]		.092
0 - 3	185 (70)	
4 - 6	67 (80)	
Occurrence of previous surgeries		.498
Yes	74 (70)	
No	182 (74)	
Location of informed consent[2]		.416
Outpatient Clinic	166 (72)	
Inpatient	90 (76)	
Title of informed consenter		<.0001
Clinical research coordinator	116 (77)	
Clinical research nurse	69 (59)	
Physician (MD)	71 (86)	

Notes. [1]For the purpose of the analysis, RACHS scores were dichotomized into two groups, 1-3 and 4-6. [2]Patients who were approached for informed consent in all inpatient areas (non-ICU, NICU and PCTU) were grouped together.

The variables of age, location of informed consent, presence of a chromosomal anomaly, presence of premature birth, and whether the patient had a previous surgery had no significant association with whether or not the patients' parents consented to their child's participation in the study. Although the patients' races did not have a significant association either, African-American parents were less likely to enroll their child in the study. Only 63% of African-American parents that were approached consented to the study, while 74% of White parents consented and 73% of 'Other' parents consented. The title of the consenter was significantly associated with successful informed consent ($p<0.0001$). Parents were more likely to consent to the study when approached by the study physician or the clinical research coordinator than the study's clinical research nurse.

Based on the biostatistician's professional preference, a p-value of .2 or less was used to determine which variables qualified to be analyzed in a multivariate analysis. Centered on that criterion, sex, title of consenter, prenatal diagnosis and RACHS score were further explored.

Multivariate Analysis

A multivariate logistic regression was used to determine if variables from the univariate analyses (sex, title of consenter, RACHS score, and prenatal diagnosis) could be independent risk factors for successful consenting (Table 5). Furthermore, a pairwise comparison of the title of consenter was made such as 'physician vs. coordinator', 'physician vs. nurse', and 'coordinator vs. nurse'.

Table 5

Multivariate Analysis of Associations Between Sex, Title of Informed Consenter, RACHS Score, Time of Diagnosis and Successful Consenting

	Odds Ratio	(95% CI)	p
Male vs. female	1.6	(1.0-2.7)	.063
Consenter			.0001
Physician vs. clinical research coordinator	1.1	(0.8-1.6)	.502
Physician vs. clinical research nurse	2.2	(1.5-3.1)	<0.001
Clinical research coordinator vs. nurse	2.4	(1.4-4.2)	.001
RACHS score (4-6 vs. 1-3)	1.5	(0.8-2.9)	.176
Post- vs. pre-natal diagnosis	1.5	(0.9-2.4)	.142

According to the multivariate analysis, the individual who performed the consent was a significant independent risk factor of successful consenting, controlling for other variables (p=0.0001). Although there was not a significant relationship between the physician and clinical research coordinator as to whether or not the parent consented to the research study, parents were 2.2 times more likely to consent when approached by the study physician than the clinical research nurse ($p < 0.001$) and 2.4 times more likely to consent to the study when approached by the clinical research coordinator than the clinical research nurse (p=.001). Although parents of male patients were 1.6 times more likely to have their child participate in the research study than parents of female patients, gender of the patients was not a significant independent risk factor (p=.063)

Chapter 5: Discussion

According to the results of this analysis, the only variable that had an influence on whether or not parents consent to their child's participation in research is the title of the consenter performing the informed consent. Although there was no difference between the physician and the coordinator performing the consent, parents were significantly more likely to consent to a research study when approached by the physician versus the research nurse, as well as when approached by the clinical research coordinator versus the research nurse. This could be because parents do not want to disappoint their physician, or they may have placed a greater amount of trust in the physician versus the research nurse. In addition, they may have felt that participating in the physician's clinical research trial may have provided them more favor when it came to the physician treating the child post-operatively. This is consistent with my previous hypothesis that parents would be more likely to consent to their child's participation in research when approached for the study by the study physician. However, I did not predict that parents were more likely to approve of their child's participation when approached by the study coordinator versus the study nurse.

My other hypotheses were proven to be incorrect: parents of younger patients were just as likely to consent to the research study as parents with older children. Although Africa-American parents had a lower rate of consent to the research study than White parents, the difference was not significant; however, this could have been due to the small sample size and limited demographic diversity. The location of the informed consent presentation had no effect on whether parents consented their children to the study, suggesting that informed consent can be successfully obtained in both inpatient and outpatient settings.

Parents with children who have chromosomal anomalies were just as likely to participate in the study as parents with chromosomally normal children. Since this study was strictly a pediatric cardiology therapeutic study and did not have a specific component relating to developmental disorders or genetic disorders, this is reasonable. Furthermore, parents whose children were diagnosed with their heart defects before birth were also just as likely to have their child participate in a study than parents whose children were diagnosed after birth. This suggests that although parents with pre-natal diagnoses of a congenital heart defect may have more time to adjust to the diagnosis and may know what to expect when it comes to their child's hospitalization, it does not have an effect when it comes to considering having their child participate in a research study. Parents of more severely sick children were slightly more likely to have their children participate in the trial than parents of less severely sick children, but the relationship was not significant. This correlation could be due to the fact that parents with sicker children are more willing to try any new therapy that could possibly provide benefit and assist their child during their hospitalization.

Chapter 6: Conclusion and Possibilities for Further Research

The findings associated with this project are somewhat consistent with previous research performed on the topic. Similar to the results of Tait et al (2004), parents of patients were more likely to consent to have their child participate in a clinical trial when the informed consent process was performed by a physician. However, my findings were inconsistent with other literature on the subject. I did not find that African-American parents were statistically less likely to enroll their child in a research study than White parents. Furthermore, I did not replicate the results of Troung et al. (2004) by finding that parents were not any more likely to enroll their child in a study if the informed consent process was performed in an inpatient setting versus an outpatient setting. In addition, my results were not consistent with previous literature in that the child's health status at the time of the informed consent did not have a significant effect on the parents' decision to consent to their participation in the clinical trial.

Although I did find a significant relationship between the title of the consenter performing the informed consent process and parents' decisions to enroll their child in a research study, it is difficult to extrapolate and generalize these results to the general clinical research world. The personalities of the different members of the research team may have had an impact on whether parents wanted their children to be in the study as well as their appearance or general demeanor. Furthermore, the results of the study could have been a result of the individuals performing the consent rather than their professional title. Due to the relatively small sample size of the study population, more research is needed to determine if the title of the consenter or individuals themselves have an impact on consent rates for pediatric studies in other therapeutic areas besides pediatric cardiology

Another limitation of this project is that because the study population consists of parents approached for consent for only one specific study, the results of this project may not be able to be extrapolated to other pediatric studies. Parents may be more likely to consent their child to a study that may involve a different therapeutic intervention, or possibly no intervention at all. The factors that influence parents' consenting to research could vary with studies of different risk levels, therapeutic areas and randomization and treatment procedures. Also, since parents were not asked their reasons for either consenting to or declining their child's participation in this study, other variables that were not investigated such as risk-benefit analysis or their understanding of the study could have had an influence on their decision-making process.

Although this project provided preliminary information regarding what kinds of factors might influence parents' decisions to enroll their child in a research study, further research with larger study populations and more diverse personnel conducting the consent process in different therapeutic areas is needed to determine if these relationships can be generalized to the general clinical research field. If there are relationships between informed consent processes and consent rates for pediatric studies, investigators and clinical research staff can uniformly optimize their consent procedures in order to generate a higher participation rate in these trials.

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