AN URBAN BIOETHICS APPROACH TO PARENTAL INFORMED CONSENT FOR PEDIATRIC CLINICAL RESEARCH

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ABSTRACT

In the current healthcare landscape, parents generally make decisions regarding whether or not their children are allowed to take part in clinical research, with the general assumption being that parents know what is best for children. Investigations have been conducted regarding what is likely to lead parents to consent or not consent to their child's participation in a trial, but research plans seldom incorporate the consideration that not all parents come into the consent process with equal social, academic, and economic footing. Since the burden of the ultimate decision lies primarily on the parents, it is supremely important that they are capable of making a well-informed and thoughtful choice. Bioethical understanding of the influence of parental decisions in clinical research must consider demographic variables and how they may affect parents' decisions to allow or disallow their child to participate in a clinical trial. Those differences could affect the consent process and have ramifications for the research findings, as research results are affected in numerous ways by which children do, and do not, participate in studies. This paper looks specifically at parents in the process of informed consent for pediatric research, taking into account several social determinants of health and how they affect who participates in research and how that affects research as a whole.

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CHAPTER 1: HISTORY

1.1 pre-Nuremburg

Finding a balance between protecting the best interests of children and the benefits of research on children for science is a concept that has been explored at length over time, but has continued to prove difficult. For example, at the end of the eighteenth century, Jenner first tested his smallpox vaccine on his one-year-old son. In 1885, 9-year-old Joseph Meister was first human recipient of Louis Pasteur's anti-rabies vaccine, after his mother begged Pasteur to conduct the trial. He consulted first with two other physicians, who determined that Joseph was at high enough risk for illness after having been bitten by a clearly rabid dog, proving that this was an instance in which Pasteur truly believed the trial would have direct benefit for the subject.

In the late 19th century, the only thing governing medical research was the consciences of the physicians and scientists who were conducting the experiments. Research was continually carried out on all forms of human subjects, but there were no specific guidelines for protecting those who were more vulnerable, such as those who were imprisoned, the mentally infirm, and children. These particular categories of research subjects were all under the control of superiors who had the ultimate say in their involvement and well-being. Though it was crucial to remain aware of the children's' safety, it was also essential to have them involved as research subjects, as medical conditions in children are physiologically different than those in their adult counterparts. Therefore, a balance needed to be stuck between necessity of research and responsibility for the safety of an at-risk population. The journey to find that balance is ongoing, and

over the course of the next century, much advancement was made in policy to protect this, and other, vulnerable groups.

After the Second World War, informed consent became a prominent topic of conversation in US ethicist circles. Following the verdict in the 1947 case of *United States v. Karl Brandt, et al*, which ruled against 16 physicians who performed experiments in Nazi concentration camps, the International Military Tribunal crafted the Nuremburg Code (Annas & Grodin, 1990). The Nuremburg code was the first formal international code of research ethics, and although it didn't specifically mention research on children, its emphasis on the necessity of informed consent was fairly conclusive in its excluding children from being subjects for research. Unfortunately, the existence of this 10-point code of ethics didn't halt the involvement of children in questionable research.

1.2 1950s-1970s

Between 1944-1974, "nontherapeutic" experiments with radioactive isotopes were done on children as part of a larger group of experiments known as the Human Radiation Experiments. The Human Radiation Experiments were primarily led by the Atomic Energy Commission (AEC), but numerous other government agencies were involved in their funding and activities, including the Department of Defense and the National Institutes of Health. In this particular study, scientists from Harvard University and Massachusetts Institute of Technology gave students in the "Science Club" milk laced with radioactive isotopes. They then conducted long term testing protocols, such as blood tests, to observe the results (Faden, 1994; West, 1998).

AEC researchers obtained deficient parental permission, as they provided purposefully misleading information to parents rather than truly obtaining informed consent. This consent was obtained by sending a letter to parents that stated that the school hoped to give "a group of our brighter students a special diet rich in [certain] substances," and requested a signature to confirm that the parents did not object. The letter was written in a way that suggested that these substances would be beneficial for the children, although that was not the case (West, 1998). These radiation studies exposed children to radioisotopes that ultimately were associated with unacceptable increases in the risk of developing cancer later in life. (Diekema, 2006).

Another infamous study commonly cited for questionable ethical standards took place during the 1950s and 1960s at the Willowbrook State School in New York. Dr. Saul Krugman was purposefully inoculating intellectually disabled children in the school with hepatitis in order to study the virus' natural progression. This study is particularly notorious because Dr. Krugman presented coercive offers to parents for their children's expedited admission to the school, as well as more hygienic conditions and better nutrition to patients in his special study unit (Krugman & Shapiro, 1971). Reading Krugman's personal accounts of these studies, it seems that he did indeed extend these offers, stating blatantly that participation in the project would raise the quality of life for children who participated. It has been argued that his studies were appropriate by the mores of his time, and the numerous awards he received for his work with hepatitis reflect that possibility. On the other hand, dialogue after the fact can also provide evidence that suggests the answers to many of Krugman's scientific questions could have

been found by other means, and that there are cases in which mere consent is not sufficient to consider research ethical (John D. Lantos, 2010).

The 1964 Declaration of Helsinki marks the beginning of a shift in formal understandings of research ethics regulations. This shift was not immediate, but took form slowly over the late 20th and early 21st centuries. The Declaration of Helsinki was adopted by the World Medical Association and stood as the updated set of research principles originally outlined in the Nuremburg Code. The Declaration of Helsinki in part was written in order to adapt earlier regulations in a way that would allow for proxy consent, for both incompetent adults as well as children, as the original code is written in such as way as to prohibit any research on an individual who could not provide autonomous consent, defined as being of sound mind and of adult year. The Declaration of Helsinki emphasized that "concern for the interests of the subject must always prevail over the interest of science and society," and explicitly addressed issues regarding the involvement of children in research (General Assembly of the World Medical Association, 2013). Previous to this declaration, institutionalized children were historically favored as a test group in the US, even though other nations had outlawed this type of research well before. The Declaration of Helsinki explicitly addressed the issue of consent for children in research by stating that "the physician must seek informed consent from the legally authorised representative," and "when a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative" (General Assembly of the World Medical Association, 2013).

1.3 Late 20th Century

Until the last half-century, children were commonly chosen as research subjects due to the fact that they were so conveniently available (Diekema, 2006). As discussed previously, they were easily found in clusters at schools and often had parents that did not fully understand the possible risks of scientific research. By the late 20th century, it became blindingly apparent in the United States that stricter guidelines were necessary to help protect the country's children from the hazards of unregulated studies, and new policies began to gain traction in government. With hopes for protecting some of the nation's most vulnerable subjects without excluding them from beneficial scientific discoveries, a notable shift occurred from the sharp focus on autonomy to the wider lens of the principle of "respect for persons."

In the 1970's, the need for a set of research regulations specifically for children as research subjects was formally recognized when the United States Congress called upon the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research to convene a committee with the purpose of determining and addressing the unique ethical concerns involved in using children as research subjects. In 1977, the committee published their report, *, Research involving children: Report and Recommendations*, which set ethical guidelines that both supported the need for this type of research and insisted on protecting children from unnecessary harm or risk (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1977).

Research involving children: Report and Recommendations was informed by work being done on a more general piece on human subject protection, the Belmont

Report, which was published in 1979. The Belmont Report outlined three ethical principles that still provide the framework for ethics today: respect for persons, beneficence, and justice (National Institutes of Health, 1979). With regard to children being used as subjects for research, the primary focus of the Commission was on the challenge of balancing two seemingly opposed concepts: they determined that children should not be excluded from research that may prove to be beneficial for them, but they also must be protected from risks of said research. They acknowledged the vulnerability of children as research subjects and highlighted the need for additional protections and restrictions when they were involved in research. That said, there was an undeniable need for research involving children, for to exclude them from scientific study would jeopardize opportunities for good health and well being of all children globally. They argued for special provisions for vulnerable populations, including children, the elderly, and mentally infirm, with each "considered on its own terms" (National Institutes of Health, 1979).

"If historical examples reveal the vulnerability of children to harm through medical research, the corollary vulnerability is harm through lack of participation in research" (Barfield & Church, 2005). Balancing these two vulnerabilities is the central question for pediatric research ethics—the goal is to include pediatric patients in research efforts while doing so in concert with ethical guidelines. My argument in this thesis is that we must focus more of our attention on learning to consider how to incorporate attention to the social determinants of health in our consent process in order to equitably involve children while exploring social and medical questions. Though recent decades have ushered in several new regulations, there is still much to do in order to ensure that

all children involved in clinical research are given an equal chance to be under the care of adults who understand the details behind their participation. There are many more ways that parents can be meaningfully, and not just legally, involved in the consent process, and by studying the current research on factors that affect participation in clinical research studies, it becomes possible to calculate strategy towards a future in which the system takes increasingly better care of a more equitable range of research subjects.

CHAPTER 2: CONTEMPORARY IRBS AND PEDIATRIC RISK ASSESSMENT

In clinical research, investigators must consider each individual potential participant and apply the tenets of ethical research to determine if the trial is in the best interest of each participant. As physicians and researchers, there is a duty to "do no harm," and that is what makes the level of risk for each trial so important to consider. This is particularly important when dealing with the pediatric population, where adult clinicians and caregivers are in charge of determining whether or not the trial is safe and appropriate enough for the participant to partake.

While all research must fit into a certain ethical framework, studies involving a pediatric population face a stricter set of guidelines. The foremost governance of pediatric research is to always choose the path that is most beneficial to the individual child (Commission for the Study of Bioethical Issues, of Health, & Services, 2013). The child's caretaker and the medical professionals involved in research each may have a unique perspective on what is most aligned with the child's welfare, and those opinions must harmonize in order for true consent to be achieved. Considerations for studies that involve children as research subjects always include involvement of the three basic ethical principles published by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research: respect for persons, beneficence, and justice.

Respect for persons in cases involving children requires acknowledging the child's lack of decision-making autonomy and ensuring that their caretakers are provided with sufficient, accurate information to use while making decisions for the child.

Beneficence can be broken into two parts: the Hippocratic concept of "do no harm," and the practice of maximizing research benefits for the child, while minimizing potential harm. Maintaining justice in research entails considering who reaps the benefits of the increased knowledge from the research and who bears the burdens acquired in the process. A just study balances on the delicate line between advancement of science and the potential risks involved in the process of discovery (Barfield & Church, 2005; Diekema, 2006; National Institutes of Health, 1979).

Federal regulations outline four categories of risk levels in pediatric research: 404, research involving no greater than minimal risk; 405, research with a prospect of direct benefit but with greater than minimal risk; 406, research involving greater than minimal risk with no prospect of direct benefit, but that is considered worthy and ethical for the generation of generalizable knowledge; and 407, research not otherwise approval, but with the possibility for important gains in knowledge. The level of risk assigned to different research protocols can vary based on the investigators and IRB who analyze the studies.

The first level of risk, 404, is the designation given to trials that are considered "minimal risk,' which is generally determined as risk that is lesser than or equal to the level that a child would encounter in their everyday life. Under current guidelines, studies with minimal risk and no potential benefit to the child can be performed with permission from one parent and the child's assent, if they are cognitively capable (Laventhal et al., 2012). "Risk" is not a straightforward concept, however, considering that researchers are constantly working with different populations of children. Care must be taken to be sure not to compare different populations when analyzing potential risk for a study. For

example, a series of blood draws, which is generally regarded as low risk for an otherwise healthy child, could potentially be a death sentence for a child living with clotting problems or immune system dysfunction. It must also be considered that the daily life of the average child has high potential for risk, but those types of risk can be different than those encountered under study conditions. For example, the risk level of climbing a tree or riding a bike is different than the risk incurred during a blood draw.

The second level of risk, dubbed "minor increase," is fairly self-explanatory. Usually this advanced level of risk will negotiate the amount of advance risk versus the potential for benefit to the subject. Unlike with the first level, with this increase in risk, there must be an equal increase in potential benefit directly for the child who is participating in research. In many cases, the opportunity for benefit outweighs the risk to the patient, and the ethical conclusion is to encourage that the patient participate in the research. The next two levels of risk involve risk that is greater than a minimal increase, but either with or without direct benefit to the child participant. Approving research that risks harm and holds no potential benefit is a decision that requires navigating the challenging concept of participating in research for "the greater good," and whether that is appropriate to decide on the behalf of a child. For either of these types of trials, consent is necessary from both parents and assent is required if the child is capable. It is to the question of how particular parents weigh risks and benefits that I now turn.

CHAPTER 3: INFORMED CONSENT - PARENTAL CONSIDERATIONS

Institutions approving a study is only the first step in a research protocol; the second steps involve the recruitment of participants. Following the ethical guidelines reiterated in the Nuremburg Code, Declaration of Helsinki, *Research involving children: Report and Recommendations*, and the Belmont Report, considerations that must be built into an informed consent document and process include freedom of choice to participate, availability of and access to complete and understandable information, confidentiality, and assent of the child if appropriate. I will discuss each of these considerations in detail, as they will become central to my later arguments about the need for greater inclusion of consideration of social determinants in the informed consent document and process.

1.1 Free Choice

Individuals considering participation in clinical research *should* be completely free to refuse to sign informed consent documents but there are multiple factors that may hinder that freedom. The obvious first consideration is that there may be no coercion involved in the informed consent process. Parents may feel as though their child will not receive adequate care if they do not allow them to participate in research, and those concerns must be assuaged immediately to ensure that free choice be exercised in a parent's decision making (Leibson & Koren, 2015). Furthermore, there are numerous potential inconveniences to a family that has a child participating in research, and most clinicians agree that families should be compensated for their time and efforts in some

way (Kimberly, 2006). This considered, it is important ensure that this compensation is not an inducement or reward for participation, as that may lead to consent that is motivated financially and not ethically.

1.2 Complete and Understandable Information

The plan for a research study should be well explained during the informed consent process in a complete way that is understandable to those considering participation. Details, including risks and benefits, should be explicitly stated and acknowledged in consent information, as well as information regarding what procedures are and are not routine parts of the patient's care (Leibson & Koren, 2015). There are several factors that make this more difficult for researchers, including primary language of participants and the spectrum of comprehension and understanding of adults with different educational and socioeconomic backgrounds. This leads the discussion into the realm of health literacy, which will be addressed in detail in forthcoming chapters.

1.3 Confidentiality

Confidentiality is also very important in pediatric research, just as it is in research that involves adult subjects. The privacy of research subjects' personal and health data should remain the most important consideration in clinical research (Leibson & Koren, 2015). All confidentiality measures should be outlined in consent documents.

1.4 Assent

Typically, guardians give proxy consent for clinical research of children. Assent is often also a factor in the full consenting process, and though there is currently much discussion involving the age a child is capable of giving assent, the general concept itself is relevant to the discussion here. Leibson defines assent as a process and document that explains to the child in language s/he can understand the essence of what is planned in the research, as well as the fact that s/he can say 'no', or can change his/her mind midway through the research" (Leibson & Koren, 2015). A stand-alone assent document lacks the legal and technical information that is contained in the full informed consent documents, but is an essential part of research that involves young people who are capable of making informed decisions about their own care. Studies on the capacity of children to understand research information have yet to agree upon an age at which assent must be obtained, but it is still a consideration that must be made while gathering consent documents. This analysis is parent facing and does not delve deeply into the concept of assent.

CHAPTER 4: SDH AS BARRIERS TO INFORMED CONSENT

Even with all of the aforementioned factors considered, the field of bioethics still has a long way to go in determining the best ways to inform adults during consenting procedures, especially when they involve signing consent for a child's participation. This is where the social determinants of health become relevant to the discussion. In the current healthcare landscape, parents are primarily the ones making the decision regarding whether or not children are allowed to take part in clinical research, with the general assumption being that adults know what is best for children. Investigations have been done regarding what is likely to lead parents to consent or not consent to their child's participation in a trial, but it is not always considered along with the thought that perhaps not all parents come into the consent process with equal social, academic, economic footing.

Since the burden of the ultimate decision lies primarily on the parent, it is supremely important that they are capable of making a well-informed and thoughtful choice. Bioethical understanding of the influence of parental decisions in clinical research must consider demographic variables and how they may affect parents' decisions to allow or disallow their child to participate in a clinical trial. Some of the main barriers to adults' true understanding of the informed consent process include health literacy, socioeconomic status, and cultural norms. Differences in those three categories (and many others,) could affect the consent process and have ramifications for the research findings, as research results are affected in numerous ways by which children do, and do not, participate in studies.

Health literacy, socioeconomic status, and cultural norms are three major factors that have been identified as potentially putting a parent at risk of enrolling their child in clinical research without fully comprehending the implications of participation. (Barfield & Church, 2005) These factors should always be considered, but are especially important in urban environments, where populations tend to have high variation in backgrounds and social status. Here I turn to the interrogation of audiences through a lens that takes into account several social determinants of health and how they affect who participates in research and how that affects research as a whole.

1.1 Health Literacy

Written consent forms constitute an important part of research studies, as they serve to both inform the participant and cover liabilities for the research bodies. As time goes on, the length and complexities of these forms has become an issue, bringing health literacy to the forefront of research considerations. The term "health literacy" is used to define the level of a person's understanding of health-related information when it is presented in non-medical terms. The discussion of health literacy often dovetails with conversation surrounding informed consent. Some of the key criteria for informed consent include discussion and comprehension of the risks and benefits of the research, reviewing numerous rights of the patient, and concepts behind the research, such as randomization. Communicating this information often requires a higher level of health literacy than can be found in the general public, creating a barrier to understanding both how the research works and what the patient is agreeing to by signing the documents.

Literacy standards for informed consent forms have been set by numerous groups, including the large scale Office for Human Research Protections (OHRP) and local Institutional Review Boards (IRBs) and are recommended to be set between a sixth and eighth grade reading level, as that is the level of the average American layperson according to the National Institutes of Health (Foe & Larson, 2016). Issues remain, however, with the level of comprehension reached by patients with current consent forms (Larson, Foe, & Lally, 2015). A study conducted in the emergency department of a US medical center reported that 25% of adults studied had a level of health literacy that was in the range of marginal to inadequate (Carpenter et al., 2014). Furthermore, a recent review of studies estimated that currently, 14-22% of American adults are considered functionally illiterate, deeming overall adult ability to read consent documents incredibly variable (Leibson & Koren, 2015). This review also found that that pediatric research has some of the lowest grade level readability, yet is still usually above the literacy level of the average American adult.

The Flesch-Kincaid grade level readability formula was created to determine the readability level of a text by comparing it to a grade relative to the US school grade level. According to the National Institutes of Health (NIH,) the average Flesch-Kincaid reading level of an adult in the United States comes in at the sixth to eighth grade level, and consent documents are supposed to be written with that consideration (Foe & Larson, 2016). Numerous studies have found that is common that they do not, which affects their decision-making in ways that must be ethically considered by those requiring parental consent to conduct research on children. Studies have shown that length and complexity

can be a disincentive to reading documents in their entirety and tend to leave individuals on the patient end of the consent process feeling overwhelmed and frustrated.

Information needing to be expressed in consent forms is often complex and requires higher health literacy levels to be understood. In addition, details are often included on forms for liability purposes, rather than to enhance the potential participant's understanding of the research (Larson et al., 2015). Having adults consent for children's participation in research constitutes a hazard that goes beyond just affecting the adult, as it also affect the child. Without more attention to literacy, as well as to medical and scientific literacy, there is significant risk that parents can be making choices regarding consent to their child's participation in research without being fully prepared to do so.

1.2 Socioeconomic Status

The highest level of education reached by parents makes a statistically significant difference on whether or not parents fully understand the consent process and therefore affects their decision regarding allowing their child to participate in clinical research. A multivariate analysis conducted in 2007 showed that parents with lower educational levels had lower comprehension levels of the key pieces included in the consent process, including understanding the randomization process, blinding, and right to withdraw (Breese, Burman, Goldberg, & Weis, 2007). Understanding these concepts is paramount to true comprehension of a study's methods, thus they are often used as indicators of true understanding in research settings. With low levels of comprehension connected to low educational achievements, this becomes a serious concern for the individuals responsible for the informed consent process.

Surveys continue to show that having graduated from college is typically associated with a lower likelihood of providing consent, and less educated individuals are more likely to give consent to participate in clinical trials (Hoberman et al., 2013; Tait PhD., Voepel-Lewis MSN. RN., & Malviya MD., 2003). This finding stayed consistent over the course of several analyses in various fields of study and has become a cornerstone in understanding what influences adults decisions during the consent process. Ethically speaking, it is essential that researchers are aware of this connection, and it is also important that governing bodies moderate studies to guarantee this fact isn't exploited to gain study participants, as it was in Dr. Krugman's research at the Willowbrook State School.

Issues with consent related to communication and comprehension are also common in parents with limited English proficiency. Language barriers only widen the gap in understanding created by health literacy issues. Primary language is deeply intertwined with social position and educational level, typically with the latter two being lower as the language deficit increases (Ford et al., 2013). There is frequently a lower level of understanding of the consent process for those parents who don't speak English fluently, and that leads to inequity in clinical research. This is even seen in studies that have adapted their communications to be accessible to speakers of non-English languages; often the level of translation is not as clear as the original text, missing key pieces of information, or uses the wrong words to express the originally intended concepts (Ford et al., 2013). Though grant funding does not always cover translation services or hiring of multilingual staff, at this point, the lower level of textual understanding can be viewed as fault of the research team rather than cultural differences

and suggests a lack of consideration for potential subjects with different language backgrounds.

In a study done on comprehension of the consent process for parents enrolling their child in an alternative treatment for leukemia, it was found that English speakers actually received 6% more details about the treatment, and non-English speaking parents asked approximately half as many questions compared to those who went through the consent process in their native tongue (Simon et al., 2003). In this study, overall social position of each participant was calculated with the Hollingshead Two-Factor Index of Social Position, which bases placement on a scale on occupation and educational level (Adams & Weakliem, 2011). This study found that issues with consent-related communication and understanding were more frequent among parents of low social status who spoke little or no English (Simon et al., 2003). Two thirds of the non-English speaking parents were found to have not completed high school, which added a potential knowledge deficit to the already present language barrier.

Income level and insurance coverage go hand in hand in today's society, and both are social determinants of health that can affect the consent process and therefore the field of clinical research as a whole. Often, research studies will offer some sort of compensation for time, travel, and other inconveniences that may be encountered by participating in the study. This is frequently deemed risky, and when coercion becomes a concern, it is encouraged that researchers opt to offer smaller compensation and reach out to a larger population in order to maintain high levels of ethically appropriate consent (Acharya, Norton, & Lumeng, 2017). While there are many recommendations put forth regarding how to determine what level of compensation is appropriate and not considered

coercion, the fact remains that better compensation likely begets more involvement in the study (Friedman, Foster, Bergeron, Tanner, & Kim, 2015). Parents with a lower level of income have consistently proven more likely to consent to their children partaking in research that offers a monetary reward for participation (Acharya et al., 2017; Tishler & Bartholomae, 2002).

True informed consent includes the parent being aware of standard care practices and how the research practice will differ from the standard. Parents should be given the various care options in addition to the study protocol, and be allowed the choice to choose the option that allows their child to receive the best care possible. This frequently is manipulated by the healthcare industry to steer parents towards research participation as the most affordable option for the "gold standard" care. A study conducted in 2012 concluded that families with lower annual incomes were more likely to participate in clinical trials when offered free visits and gifts, and they also observed that access to free medication through research opportunities was more important in families with lower incomes than in families with higher incomes (Rothmier, Lasley, & Shapiro, 2003).

The issue of free medication brings up another relevant point; when a family has a lower income, receiving essential things for free, like cash or medicine, has more appeal than if the family is financially stable. Unfortunately, finances often limit medical care options for families and steer them towards participation in research as the most accessible option. This type of coercion is rampant in low-income communities where families are often forced to choose the most accessible and affordable option without knowing all their choices.

This also leads to very specific populations carrying an unequal burden of research participation, which has the possibility of directly affecting the research results. Acharya et al., in a study of parents' willingness to supply a child's blood sample based on the amount of financial compensation given, warned that researchers should "exercise caution while extending research findings to other settings," since demographic compositions of research subjects may differ from the overall composition of the U.S. population (Acharya et al., 2017). Financial gain is a confounding factor and an ethical grey area in clinical research, as it may entice underrepresented populations to participate, but perhaps for a reason deemed "unethical."

1.3 Cultural Norms

Despite the clear need for more representation of minority groups in medical research, researchers struggle to conduct ethically representative studies. In view of that fact, identifying cultural norms that serve as facilitators and barriers to participation in research has become a key goal for researchers in recent years. One particular research study summarized the current situation by noting that "insufficient representation of racially and ethnically diverse groups and women in clinical trials results in inequitable distribution of the risks and benefits of research participation and reduces the generalizability of trial results" (Pinsky et al, 2008). Studies have identified many barriers to participation in research by minority groups, most of which can be generalized in three categories: issues with certain characteristics of the healthcare system, experience with and perceptions of healthcare providers, and the preferences and attitudes of patients (Smedley, Stith, & Nelson, 2003). Cultural backgrounds and historical treatment

of certain groups determines many patients' feelings about participation in research studies.

For example, in one study conducted at five sites in South Carolina, researchers focused on African American and Latino patients. They discovered that, in general, Latinos were increasingly likely to trust researchers who spoke Spanish, and preferred documents that were accurately translated into Spanish, especially for low-literacy levels. Attitudes towards researchers were colored by observations regarding the individual's intentions for the research; this subgroup of patients was particularly aware of whether or not the researcher had the best interests of the patients at heart and was sensitive to any indications that the medical team was mainly "in it for the money" (Ford et al., 2013). Members of the Latino community also suggested that it become routine for researchers to reinforce the idea to patients that participation in research would not document immigration status, nor would said status prevent participation.

It has been found that African Americans generally think that the burden of medical research isn't shared equally among racial and ethnic groups (Luebbert & Perez, 2016). In this cultural community, research reflects a strong attitude of mistrust regarding medical and scientific research (Corbie-Smith, Thomas, & St. George, 2002; Luebbert & Perez, 2016; V L Shavers, Lynch, & Burmeister, 2001). Patients fear that researchers will not take the time and care needed during the informed consent process to to explain everything involved in the trials. Patients fear that instead of researchers keeping the best interests of study subjects in mind, they will rather use patients as "guinea pigs" for scientific gain. This is often based specifically on historic recollections of unethical research done in this population by medical and scientific communities, referencing such

events as the Tuskegee Syphilis Trials and research done on enslaved in the nineteenth century (Ford et al., 2013; Luebbert & Perez, 2016; Shavers, Lynch, & Burmeister, 2002). Fear and mistrust in the systems that should be put in place to keep them safe and healthy represents a large failing of the medical ethics system in the United States, and there is much to be done to regain trust from these underserved populations.

CHAPTER 5: CONCLUSIONS

The informed consent process has continued to grow and change in recent decades, as science and medicine attempt to keep up with a dynamic society. The ethics underpinning pediatric clinical trials have flourished from being a few sentences added to the end of protocols for adults to being an individual, robust topic of study. The next steps in this process should involve consideration for parents' role as decision-maker during informed consent for pediatric clinical research and how that role is influenced by the social determinants of health. For all the scope of things discussed, the key underlying ethics are focused on levels of risk, complete and understandable information, confidentiality, assent, and most importantly, freedom of choice. Each one of these factors is a gateway for parents to become more meaningfully, and not just legally, involved with pediatric research.

Health literacy is a main factor used in distinguishing whether or not informed consent documents are appropriate so as to be meaningful, and there is still a long way to go in order to reach the goal of every patient having acceptable comprehension of standardized documents. Socioeconomic status is another primary consideration in research ethics, specifically how education level, primary language, and income levels of parents affect consent. The choices made by parents through the lens of those three determinants dictate not only which individual children participate in research, but to the larger breadth and scope of research findings which communities are affected by or have access to those discoveries. Finally, cultural norms often serve as a barrier to ethical informed consent. Different communities have varying views of and requirements for

research processes, making it difficult to include all groups equally and spread the benefits of research as much as the burdens.

Though guidelines for ethical decision-making in the field of pediatric research have already advanced substantially, the need for progress remains. Striking a balance between considerations for the safety and well-being of children and continuing the research that focuses on keeping them healthy is a challenge that will always be present, just as change in the world's circumstances will always be reliable. Applying the principles of bioethics is one of the most fundamental tools that physicians and scientists have when approaching these issues, and as long as they use ethical principles as the underpinnings for their research, progress in the future is guaranteed.

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