Boundaries, Limitations and the Parental Perception of Newborn Research in the Neonatal Intensive Care Unit

by

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Abstract

The Newborn ICU (NICU) has long been a very fragile environment to obtain consent for clinical research trials. In an overwhelming environment, the interest was to investigate parental insights upon solicitation for research consent. Perceptions relating to timing of consent, presentation of information, and the request for multiple trial enrollments are the key aspects identified. Methods included searching various academic search engines using the term "parental consent in neonatal research". The search focused specifically on research done in the NICU population with critically ill neonates. Results found that while parents agree with allowing their newborn to participate in research, timing and presentation of the clinical trial plays a key part in obtaining consent. No parent wants to feel as though their baby is going to be used for a plethora of research simply by their entrance to the NICU. Consideration for the parents needs to be addressed on the part of the researcher obtaining consent and in the care of the neonate.

Introduction

The neonatal period has long been perceived as a tenuous time to approach parents for participation of their infant in a clinical trial, especially in the intensive care setting. Parents are overwhelmed and coping not only with the realization of becoming parents, but also with the possibility of a critically ill newborn. With much to be learned in the critically ill neonate population, the potential to enroll a baby into multiple trials in a neonatal intensive care unit is always a possibility.

Fisher *et al*. (2011) found that the parents understanding of information given to them during the consent process may be limited. It is found that parents feel vulnerable with a sense of responsibility and fear in making the wrong decision when it comes to consenting for research. Building on this is the fact that neonatal research consent takes place early on in life, sometimes immediately after the delivery of a critical diagnosis. Parents then have to make the decision on whether or not to consent during a time when they are vulnerable and distressed, while at the same time trying to care for a sick child (Shilling & Young, 2009). Research done by Morley *et al*. (2005) concluded that ninety-four percent of the parents they had surveyed thought that if they consented for their baby to join a research study, the care for their baby in the future would either be better or exceedingly better.

The question then stands as to the appropriateness of approaching parents for consent to enroll their newborn into a clinical trial or several clinical trials. Consenting in this population is difficult given that the parents are giving consent by proxy on behalf of their newborn. The assumption is that the parents will always act in the best interest of their baby and use their best judgment (Shilling & Young, 2009). Parental decisions

come into conflict when the mental state of the parent can be inadequate to make a decision concerning research participation (Ballard *et al*. 2004). Also, many parents have not yet thought about the possibility of their infant participating in research prior to entering the hospital. This lack of preparation can contribute to the sense of pressure and lack of time to make a careful decision regarding research participation (Stenson, Becker, & McIntosh, 2004).

To obtain consent for a clinical trial, there are four components that need to be met. The consent must be free and voluntary, an informed choice is made with sufficient information given, the understanding of the consenting individual (in regards to the research study) has to be sufficient to make an informed choice and finally, the consenting individual has to be mentally competent (McKetchnie & Gill, 2006). It is questionable as to whether obtaining consent from a parent of a critically ill neonate for research meets all these criteria (Golec *et al*. 2004).

Consent for research in the neonate population falls into three separate classifications: Emergent, meaning immediate intervention; Urgent, classified as interventions that could be potentially lifesaving; and Non-Urgent, time to obtaining consent for research could be several days (McKetchnie & Gill, 2006). In the neonatal population, there is always the possibility that a single baby could be eligible for a clinical trial immediately after birth. That same baby tends to be eligible for several more non-urgent trials throughout the length of their NICU stay. The question then lies with how the entire research process affects the parents throughout the course of their baby's hospital stay; as well as what influences parents' participation to give or refrain from giving consent.

The purpose of this research is to investigate the many different perspectives of the research process in a population of critically ill newborns. As opposed to introducing yet another trial/consent in the Neonatal Intensive Care Unit (NICU) parents, I chose to research previously conducted studies and draw possible conclusions based on that information. Also, working as a coordinator in a busy NICU with 19 actively-enrolling research studies has given me a unique perspective on the consent process and parental perceptions of research. I chose to focus this research on several different components of the consent process as well as the entire view of research itself.

The main components focused on the following:

- Views and attitudes
- Consenting
- Consent timing
- Presentation of information
- Multiple Trials
- Health Care Provider
- Socioeconomic Status (SES)/Race

Methods

Using three separate search mechanisms, I obtained the desired articles with the appropriate relevancy. The most applicable search term used was "parental consent in neonatal research". I further reviewed the articles for the desired information pertaining to my search. Many of the searches between sites produced duplicate results. I also looked to remove those articles that focused on research in a healthy newborn. My

general thoughts were that if I included papers regarding research in healthy neonates, the parental perception would be different as compared to parents consenting for research in critically ill newborns. The search via PubMed yielded nineteen initial results, after reviewing for the desired content, I was only able to use thirteen that pertained to my points of discussion. Using Scopus as the next search engine, eighteen relevant sources were obtained. I was able to omit several from the start since they were duplicates of the PubMed search. I also omitted several more that pertained to research in a healthy newborn. From there, I had twelve sources that could contribute to my discussion. To finish with my sources, I searched Web of Knowledge. Again, there were several duplicate sources from the first two searches. Other unused sources from Web of Knowledge touched on medication safety in neonates as opposed to the overall parental perception of research in their infant. From this search, I only found two of the five sources to be relevant to the results of this paper. Also, having worked as a research coordinator for the last three years, one and a half of which have been in the NICU, I will also contribute my experiences and observations of other trials to the discussion of this paper.

Results

The primary focus of this research was to obtain the perceptions of parents when it comes to the research process in the critically ill neonate population.

Views and Attitudes

Much of the previously conducted research focused on the views and attitudes of the parents approached for research consent on behalf of their neonate. Mcketchnie and Gill (2006) concluded that parents have three motivations to give consent on behalf of

their baby for research. Reasons include the improved care for future babies, a direct personal benefit, and neutrality-parents see no harm, so why not? In a study done by Morely *et al*., 93% of parents felt that their baby would receive the same or even better care if they gave permission for them to be included in a clinical trial. This can also be misconstrued as "therapeutic misconception", where even the mere idea of enrolling a baby into research will improve the care they receive (Ballard *et al*. 2004). More often than not, facing a potential NICU admission for their newborn, the thought of doing anything is a better option than doing nothing. In research done by Ward (2010), parents are asked for an interview relating to their babies admission after their babies are discharged from the NICU. Faced with a situation that left them little control, parents pointed out that doing something was better than doing nothing. Parents become overwhelmed with the idea of not only becoming parents, but also having a newborn with a life-threatening issue (Thomas, 2005). Presentation of clinical information is digested at a rapid speed with little or no time for processing. This also is the case when it comes to the introduction of research.

Motivations for parents not to consent for research as illustrated by Mcketchnie and Gill (2006) are the idea of the risk of the research being too great, parents holding anti-experimental beliefs, and the manner in which the clinicians approach the parents for research participation. Fisher *et al*. (2011) concluded that those parents who did not wish to participate stated that they were not comfortable with the unknown risks of the therapies presented and they wanted to protect their child from these unidentified risks. Other identified reasons for refusal in the neonate population as identified by Mason and Allmark (2000) were the perceived risks or further distress to the baby, the distrust in the

research or the researcher themselves, displeasure with the presentation of the research by the doctor, shock and inability to decide, and the difficulty with the follow up procedures.

Hulst *et al*. 2005 concluded that severity of illness did not play a factor on whether or not a parent consented for observational research in their child. Parent's perceived the potential benefit to the overall population as a factor for allowing consent for research in their neonate. Many parents also stated that there was no perceived risk of harm in allowing their baby to participate (Hoehn *et al*. 2005).

Consenting

Diekema (2009) concluded that consenting parents for research should be viewed as a process, rather than just a single event. Parents need to be aware that they can withdraw their participation at any time and that the person seeking consent should be an individual who knows the research and is able to answer questions that pertain to the research. Ward (2009) came to the conclusion that parents relied on the information presented by physicians rather than the specific wording within the consent. This justifies the need for open communication with the study team for the duration of the babies NICU stay. Keeping lines of communication open ensures parents fully comprehend the research that they have volunteered for. Allmark (2003) makes mention of using a step process for consent, thereby reducing the amount of information parents need to process. This involves giving parents a bare minimum of information (most relevant for them to understand) before enrolling their baby into a clinical trial. As time goes on, more information is presented and if required, additional consents are obtained.

Consenting becomes intricate when it is used in conjunction with 'Zelen' randomization; this is where trial randomization occurs prior to discussing a clinical trial

with parents. Once randomization occurs, parents are approached for consent for the appropriate trial arm. Should parents refuse; the baby will then be treated with usual clinical care. Allmark (1999) concluded that 'Zelen' "pre-randomization" solves the problem of poor communication and limited choice by giving the parent less communication and choice. Burgess *et al*. (2003) concluded that parents were not thrilled with the process. Parental concerns regarding 'Zelen' pre-randomization highlighted their concerns of the healthcare team withholding information, the effect of decision-making, and the use of their baby's healthcare information without their knowledge.

Consent Timing

In keeping with the consent theme, the concern of timing of consent is also a problem in the NICU population. The NICU environment as a whole raises concerns on whether or not parents fully understand consenting for research. Most of the time, when parents are approached for consent, they are coming to terms with having a critically ill neonate. Severely stressed parents may not be thinking clearly at the time. Parents in a study done by Hoehn *et al*. (2009) commented on the fact that the study itself did not stress parents as much as the lack of time to fully understand the research and make an adequate decision regarding participation. This again brings up the issue on whether or not consent is actually valid. McKetchnie and Gill (2006) concluded that the time given to parents to consent for research is too short to obtain a valid consent. Korotchikova *et al*. (2010) found that approaching both parents together in the early post-natal period increased the likelihood they would consent to a non-therapeutic trial.

The lack of time to make a valid informed decision is also a factor in the neonatal population. Parents are attempting to digest the severity of a new diagnosis while being

approached for research that they may not fully comprehend. Ward (2009) found that parents indicated confusion surrounding their baby's NICU admission in conjunction with the presentation of a research trial. Hoehn *et al*. (2009) also commented that some parents reported that inadequate time to digest the research information prevented them from making an educated choice about participation in research. The suggestion was for further research to explore how parents under the specific time limitations in the NICU process information.

As a means of increasing compliance and allowing parents more time to digest each study, antenatal consent could be viewed as a way to increase future trial participation. This may not be the most appropriate solution, consenting in the antenatal period may add unnecessary stress to the parents (Mcketchnie & Gill, 2006). Furthermore, approaching a family for a research trial that their infant is not yet eligible for asks them to redirect their attention to something that is not yet relevant and may never be (Golec *et al*. 2004).

Presentation of Information

Care and consideration needs to be a factor when it comes to the presentation of a research study in the NICU population. It is unreasonable to assume that everyone possesses a medical background and are capable of digesting not only the clinical information but the research information as well. Findings by McKetchnie and Gill (2006) demonstrated that parents often have difficulty with the concepts and the language involved in research studies. Many find it challenging in understanding the concept of randomization and feel that should their baby randomize to standard care, they are missing out on beneficial treatment. Furthermore, the use of the word 'trial' may indicate

that there is a period of "trying out" an accepted treatment, rather than an experimental one (Franck, 2005).

Franck (2005) also observed that parents often misunderstand what it means to enroll their baby into research, citing the complexity of the information presented, stress, and the way the information is presented to them. Considering that it is such a vast amount of material to digest in a relatively short period of time, the use of information sheets may be helpful in answering parental questions. Allmark (2003) suggests the use of a "trial-specific" checklist that details the specific points of the study and the risks/benefits that may be involved. The researcher can use this tool to educate parents and answer questions before parents reach a decision on whether or not to consent. This would be extremely helpful given the stressful environment surrounding the NICU, considering that outcomes by Singhal *et al*. (2009) found that a large percentage of parents were unaware of the risks involved with trial participation.

As found by McKetchnie and Gill (2006), many parents were unaware of the involvement of an ethics committee when it came to clinical research. Many would have felt more at ease making a decision regarding trial participation had they had access to this information before the initial conversation regarding clinical trial participation.

Multiple Trials

Nearly every primary investigator has the idea that their trial is the most important. Considering that the NICU houses a comparatively small population, there becomes the push to enroll all babies that meet criteria for any given study. Golec *et al*. (2004) made the point that parents are continuously processing information related to the clinical care of their newborn. Should parents be petitioned for more than one study at a

time, they can harbor feelings of unnecessary confusion and aggravation. The authors recommend that if parents are in the process of deciding upon one study, they should continue to be able to process that information without being approached for participation in another trial.

Keeping in mind that the NICU is generally a busy environment to conduct research, Morely *et al*. (2005) discovered that a majority of parents are willing to have their neonate enrolled into several studies. Fifty-eight percent of parents were willing to give consent for 3 or more studies, 20% were willing to allow participation in 10 or more. Ultimately, 40% of parents that had agreed to research participation were happy about their infant being in several studies. Burgess *et al*. (2003) commented that parents generally do not harbor feelings of opposition to having their infant enrolled into multiple trials. However, many deemed it appropriate to only allow for participation in two trials.

Stenson, Becker, and McIntosh (2004) also commented on many parents allowing for participation of their infant in several studies. They concluded that the reasoning for this is due in part to parents becoming more familiar with the research and consent process. As they become more familiar with research consenting, the process becomes less stressful and they are more likely to remember the presented information. However, some parents commented on allowing participation into multiple trials would make them vulnerable to unintended coercion Ward (2010).

As to not overburden parents with information, timing of approach needs to be a well thought out process. McKetchnie and Gill (2006) determined that if parents are to be approached for clinical research, the requests for consent should be made at least 48-hours apart. Golec *et al*. (2004) similarly stated that multiple requests for research

participation should be timed 48-hours between each decision as to not overburden parents with information. This author also stated that parents should only be approached for research consent for their infant once in the first 72-hours of life.

Health Care Provider

The role of the health care provider is an extremely significant part when it comes to clinical research in the NICU. The health care provider can range from the physician seeking research consent to the nurses providing clinical care for the infant. Often, the nurses in the NICU are the ones carrying out the research protocol while answering questions and providing support to the parents (Oberle et al. 2000). Parents often hold the information given to them by their babies' physicians and nurses to be a very valuable asset in making a decision regarding research participation. As found by Zupanic *et al*. (1997), 32% of parents preferred that their child's physician advise them on whether or not their baby should be enrolled in a trial as opposed to deciding for themselves. Singhal *et al*. (2004) revealed that many parents in the NICU reported having trust in the physician to act in the best interest of their baby, adding that they would do as the doctor advised when consented for research. The same research found that both the physicians and nurses were confident in the research that took place at their particular institution, stating that the physicians conducting research would not place a newborn in a potentially dangerous situation. While it is clear that many parents feel confident in the information presented to them by their babies' physicians, most parents agreed that the decision to enroll their infant in a research trial should remain with the parents and not the physician (Ward, 2009). This was also true in the findings by Burgess *et al*. (2003) where in a retrospective study of parents who had enrolled their baby into a research trial while in

the NICU, 93% disagreed with the idea that the physician should be the one making the decision for enrollment.

The presentation of research by clinical staff is also another factor that can influence whether or not parents give consent for research on behalf of their newborn. It is often commonplace for any lay individual to have difficulty navigating all of the medical language that surrounds a NICU admission. This could potentially create difficulties with the consent process, as parents may not fully understand what they are consenting to. However, Burgess *et al*. (2003) found that a large number of parents (83%) stated that the physician conducting consent utilized language that was easily understandable by the parents. Parental approval for research participation can also be influenced by how they view the physician seeking consent. If the physician appears unsure of their research knowledge or does not appear to have strong feelings for the research itself, consent approval is at risk for being compromised. This was the case in research conducted by Shilling and Young (2009) where the physicians obtaining consent displayed a lack of confidence. Parents reported having an increasingly difficult time on deciding whether or not to allow participation into a clinical trial for their infant when experiencing this situation.

The consent process is the most important part of any research study; if there were no consent, there would be no trial participants. Obtaining consent is often a burdensome task for many physicians. Physicians become concerned about having their consent process observed or evaluated. Should an evaluation reveal that a physician's consent process is invalid, it may put future research endeavors for that physician in jeopardy (Ballard et al. 2004). Observations by Stenson, Becher, and McIntosh (2004) found that

due to the concern for unnecessarily increasing the parents' burden or anxiety, clinicians become motivated to give incomplete information or avoid approaching for enrollment at all. The clinicians in this study admitted that obtaining a fully informed consent placed an added emotional burden on them in addition to the parents.

As a final point to attest the importance of the physician in the context of research, agreement between physicians and specialties in the NICU must be transparent. In research done by Franck (2005) the statement is made that should clinicians lack equipoise about varying study objectives and treatments; the study can often suffer, and barriers then exist that inhibit enrollment or data collection. This is can have a damaging effect on clinical trials in the NICU as it is an environment with several clinical specialties conducting numerous research studies.

Socioeconomic Status (SES)/ Race

Many studies have attempted to answer the question on whether or not the Socioeconomic Status (SES) and race of the parents holds any influence on whether a parent will consent to research participation for their newborn. Zupanic *et al*. (1997) found there to be no significant difference between SES and race for those parents who consented to research for their newborn and those who did not. Findings in this study were comparable in the research performed by Korochikova *et al*. (2010) as well as in the findings by McKetchnie and Gill (2006).

The above-cited research found there to be no significant difference in the approval of research based on SES and race. However, Burgess *et al*. (2003) summarized that parents with less education may not have appropriate access to quality health care

and may choose to enroll their infant on the basis that they may receive better care by enrolling them into a clinical trial.

Boccia *et al*. (2009) suggests that parents put a lot of thought and consideration into consenting. This research performed to obtain parental views used the concept of a simulation, a hypothetical "what if" should parents find themselves in a given situation that may warrant research participation. The parents participating in this simulation were of a low-income classification, were predominately African American, and possessed an education level of less than high school to some college. The findings in this mock study showed that parents were very thoughtful in the decisions they made with regards to their infants participation in research. Those parents who appeared to recall more information about the risks than the benefits with regards to a highly complex procedure were less likely to accept the risk, even though there was an increased chance of extended survival for the infant.

In survey research conducted by Culbert and Davis (2005), the findings were outside of the expected population norm. Parents of babies that had been discharged from the NICU received surveys in the mail, evaluating parental preferences for hypothetical consent scenarios. The survey asked questions regarding neonatal resuscitation and clinical research trials that hypothetically would have taken place while their baby was in the NICU. Most of the respondents to this survey were married, college-educated women with a family income that was higher than the anticipated population norm. The authors made the in their conclusion that a population with a lower SES profile may yield considerably different results as compared to the results that were obtained.

Discussion

Views on research in the NICU can vary from each study and the point that each is trying to capture. Most of the research tends to agree with each other with regards to consenting, the role of the health care provider, and how and when to best approach parents. See Table 1.

Components	Current Research Outcomes
Views and Attitudes	• Parental understanding is limited during consent. Fisher *et al*. (2011) • Parents view care for baby would be better if participating in a study. Morely *et al*. (2005) • Questionable whether or not consent is valid given status of the critically ill newborn. Golec *et al*. (2004) • Parents who refused to participate in research were not comfortable with the unknown risks. Fisher *et al*. (2011) • Parents who refused participation for their baby stated refusal due to perceived risks, distress to the baby, distrust in the research or researcher, and displeasure over the way the research was presented. Mason and Allmark (2000)
Consenting	• Consent is a process rather than a single event. Diekema (2009) • Parents more likely to rely on what the physician is telling them as opposed to the specific wording within the consent. Ward (2009) • The use of a step-wise consent process is beneficial in neonatal research. Allmark (2003)
Consent Timing	• Consenting in the antenatal period adds unnecessary stress to the parents. McKetchnie and Gill (2006) • Approaching parents for research consent for something their baby is not yet eligible for redirects their attention to something that is not currently relevant. Golec *et al.* (2004) • Approaching both parents early in the post-natal period improves the rate of consent. Korotchikova *et al.* (2010) • Time allotted to parents is too short to obtain a valid consent. McKetchnie and Gill (2006) • Parents stated that the lack of time they had to fully understand a research study was stressful. Hoehn *et al*. (2009)
Presentation of Information	• Parents have difficulty with understanding the concepts and language involved in clinical trials. McKetchnie and Gill (2006)

	• Parents have a misunderstanding on what it means to enroll their baby into a research trial. Franck (2005) • Most parents are unaware of an ethics committee involvement when it comes to the approval of a clinical research trial. McKetchnie and Gill (2006)
Multiple Trials	• Parents are always processing clinical information relating to their newborn's care, this needs to be taken into consideration when approaching for research consent. Golec *et al*. (2004) • The majority of parents are willing to enroll their baby into several research studies. Morely *et al*. (2005) • As parents become more familiar with the NICU and with research itself, they may allow for their babies to participate in more clinical trials. Stenson, Becker, and McIntosh (2004) • Parents should only be approached for research once in the first 72-hours of their newborn's life. Golec *et al*. (2004) • Requests for multiple research consent should be done at least 48-hours apart. McKetchnie and Gill (2006), Golec *et al.* (2004)
Health Care Provider	• Parents trust the physician to act in the best interest of their newborn. Singhal *et al.* (2004) • Thirty-two percent of parents would prefer that their infant's physician advise them on whether or not to participate in clinical research. Zupanic *et al*. (1997) • Regardless of the advice of the physician, parents agree that the decision regarding research participation should be left to them. Ward (2009), Burgess *et al.* (2003) • The lack of confidence displayed by the physician can hinder research participation. Shilling and Young (2009) • When physicians lack equipoise, study recruitment can suffer. Franck (2005)
SES/Race	• There is no significant difference between SES and race for those who consent to research and those who do not. Zupanic *et al*. (1997), Korotchkova *et al.* (2010), McKetchnie and Gill (2006) • Parents with less education and a reduced access to appropriate health care may chose to enroll their infant in the hopes of receiving better care. Burgess *et al.* (2003)

Table 1. Summary of Literature on Neonatal Informed Consent

Approaching parents for consent for a research trial in the NICU can be somewhat of an overwhelming process for all individuals involved. The utmost care and consideration for the family must be taken into account when a parent is approached for consent on behalf of their infant. Often, parents respond better if the physician is the one

presenting the study and potentially obtaining consent. Being present in multiple situations that warranted research consent, my personal view is that parents value the time the physician takes to sit down and thoroughly explain a research study. Research wording and presentation needs to be carefully scrutinized when presenting a clinical trial to an overwhelmed parent. When taking into consideration the severity of the neonate's status, parents may not fully comprehend the complexities of a clinical trial

Working in a busy NICU with multiple clinical trials, it is advantageous for the physician who is the Primary Investigator (PI) to present the trial to the parents and answer any questions that may come about during that process. He is the resident expert with regards to the research and can typically answer more complex medical questions to the satisfaction of the parents. It is crucial to note however, that the physician obtaining consent should not be the physician providing treatment. This can create undue influence on the part of the parents and could be viewed as a coercive consent. Having one or more co-investigators on a research study can ensure that the treating physician is never the consenting physician.

After the parents have had time to digest the study, it is routinely the study coordinator that will return to obtain written consent. This typically happens in trials that are non-emergent and can characteristically take place at any time throughout the first few weeks in the NICU. Consenting becomes a concern when it is emergent or urgent research. There are times when consent takes place over the phone because the baby is in transport and the mother is still at an outside hospital. This can pose a problem at times, as the observation is that the parent(s) do not have the adequate time to fully digest and comprehend the research itself. This is somewhat unavoidable in an emergent situation

where time is of the essence. Obtaining consent from the mother immediately after delivery can be viewed as coercive, considering that one of the many factors for consent to be valid is that the consenting individual is mentally competent. This is often a gray area for a mother after delivery if she has received magnesium or pain medication. While the parent is the one who ultimately gives consent for their baby to participate in a clinical trial, it has often been helpful to give research information to the family support system. This facilitation of information is useful to keep an open dialog between the research team and the family. Many times, the father and other extended family will arrive to the receiving NICU while the neonate is in transport. Upon arrival, they typically meet with physicians and research team to get additional questions answered and to receive supplementary information. This added measure is observed to be helpful for when the mother arrives to the NICU. When a mother knows what to expect, she has a more competent understanding of the research her infant is participating in.

Step-wise consenting is also another helpful process discovered to be beneficial in NICU clinical research. Giving parents the minimum amount of information needed to obtain consent for the initial part of the research, then following up with more information and/or additional consents if needed. This type of step-wise process is currently in use with a neonatal seizure study; using two separate consents that pertain to the different portions of the trial. The main trial consent takes place on a near emergent basis when the baby has arrived to the hospital or is getting prepared for clinical monitoring. Consent for follow up information will then be obtained when the patient is close to discharge. Parents are more apt to digest information relating to long-term outcomes at the time near discharge since their baby is no longer in an emergent state.

Overwhelming parents with too much information at the beginning of their babies' NICU stay can deter future participation in research. The stepwise consent process alleviates the amount of pertinent information a parent needs to comprehend at the time of admittance to the NICU.

The NICU contains many admissions for premature babies and often houses many sets of twins and triplets. Frequently, one or more babies can take a turn for the worse and treatment becomes redirected towards palliative care. It is at this time where consent timing certainly needs to be scrutinized. At a time like this, it is not admissible to consider approaching parents for consent in a non-therapeutic trial for the sibling. As a study team, it is vital to understand the NICU environment and the status of any baby that is under consideration for a clinical trial. Keeping ongoing communication with the care team is the best way to determine when the most opportune time for seeking consent from parents is.

To avoid the difficulty in trying to obtain consent in an emergent situation or when time is of the essence, the idea of antenatal consent is potentially an option. Seeing many premature, low-birth weight babies in the NICU, there is always the risk of developing necrotizing enterocolitis (NEC). This is when portions of the underdeveloped bowel develop necrosis or tissue death. One randomized clinical trial looks at the outcomes of inserting a peritoneal drain versus performing a laparotomy as a means for treatment. Little information exists about which is the better treatment option. When this is diagnosed, surgeons and neonatologists then look to discuss the trial and possibly seek consent from the parents. Parents have the option of entering the randomized arm or the preference arm, which is ultimately the preference of the surgeon, or chose not to

participate in either. Having witnessed several of these cases, parents often remark that they do not feel comfortable having a computer decides treatment for their baby (i.e. randomization) and decline participation. Refusal of participation could also be attributed to the lack of time to review consent and digest the concepts of the study. "Zelen" randomization introduces a way to limit the amount of decisions parents need to make during an emergent situation. Previous research demonstrates that this type of approach to clinical randomization is an issue with parents; "Zelen" can also present a problem with a site's institutional review board. Obtaining consent in this manner could be perceived as coercive and deceiving, considering that a decision has already been made in some aspect and the parents now need to be agreeable to it.

Working in a large 40-bed NICU, there is the realization that every baby admitted could be a potential trial candidate. Having a better system to present clinical trials could hypothetically aid in increased trial recruitment. Many mothers get admitted for a period of time before the baby arrives and during this course of treatment, the NICU physicians perform consultations. It could be possible that after this point of contact, parents receive a brochure with research opportunities that currently take place in the NICU setting. While this again addresses the problem of burdening parents with information before needed, it does expose them to the idea of research and the types of trials that take place without specifically addressing one condition. Also, if in fact their baby becomes eligible for any given trial; there may be the recognition of already knowing a little bit about the study, making the consent process seem a little less overwhelming. Many parents are unaware of the process that it takes to approve a clinical trial for use in the NICU setting.

Adding this information to the brochure itself is yet another tool that educates parents and could make them feel at ease with the concept of clinical research.

The previous research has shown that many parents are open and agreeable to allowing their baby to participate in more than one clinical trial. This becomes a problem when there are situations where a baby is potentially eligible for up to ten studies throughout the course of their NICU stay. Case in point, our NICU currently has 10 enrolling trials that all encompass the same population of preterm ELBW (Extremely Low Birth Weight) babies. While not all of these studies take place at the exact same time point, there is still the burden of approaching parents for too much consent for research. The question then becomes when is it too much? In our NICU, out of the 10 studies that a single infant may be eligible for, 4 have the desire to seek consent within the first 24-hours of life. In the first through fourth week of life, an infant could become eligible for an additional four trials. The remaining 2 trials for this population seek consent at or near discharge from the NICU.

The potential problem with having so many research studies available for a remarkably limited population size is that it is difficult to determine priority. When parents are solicited for 1-2 studies in the first 24-hours of life, both of which fall under sample collection, they may be less willing to participate in a trial at three-weeks of life for an interventional trial. The problem also lies with the PI of each study, often having the mindset that their trial enrollment should take precedent over others. Although there have been several conversations regarding setting priority for studies, little resolution has come about. As of the current time, priority exists on a “first come, first serve” basis. Clinical judgment is often used to determine whether or not it is appropriate to approach

parents for several different studies throughout the NICU stay. Obtaining this information from nurses and the physicians with regards to the health of the infant as well as the attitudes of the parents can be helpful in determining whether or not to approach parents for another trial. Occasionally parents are more than agreeable to allow their infant to participate, but often parents feel that their baby has been through enough just by being a patient in the NICU.

Confidence in the health care staff, primarily the physician is by and large a determining factor for clinical trial consent rates in the NICU. Having witnessed several consents, the self-confidence that the physician displays can have a bearing on whether or not a parent agrees to a research study. Once the physician displays a lack of confidence in conveying the study; parents lack confidence in the trial itself. It is also crucial to note that the physician seeking consent should not be the physician treating the infant. As previously mentioned, this has the potential to create coercion from the physician to the parents. Situations such as this make it imperative that there is equipoise between the physicians in the NICU. If the treating physician is the PI on the study seeking enrollment and there is no other physician that agrees with the research to explain the study to parents and potentially seek consent, the research is null. Ultimately, for interventional studies in the NICU, the physician is the individual seeking consent.

For non-interventional trials, the coordinator is typically the one who discusses the study with the parents and obtains consent. It is extremely helpful to continue to have contact with parents long after the consent has taken place and the trial for the most part is over. Following up with them with regards to how they are doing and if they need any additional information aids in leaving a positive impression. Often, parents are

appreciative that there is continued follow-up and they and their baby were not just treated like another subject in the trial. This method has also been helpful in improving compliance rates with regards to studies that have a follow-up portion long after the baby has left the NICU. Leaving a positive impression with the family only aids in collecting necessary information long after a baby leaves the NICU.

Education by nursing regarding clinical research has been beneficial in the NICU. Nurses have the most contact with the infant and family, making them an integral part of the facilitation of the trial. Currently in the NICU there are 18 actively enrolling studies, many of which take place over a several day period. Nurses typically get asked questions pertaining to the research when the PI or coordinators are not available. Creating reference binders and education sheets have aided in helping both nursing and the parents having a better understanding of the research that the infant is participating in. The nursing staff also retains a wealth of information with regards to when it may or may not be an appropriate time to discuss a clinical research protocol with parents. They have been helpful with facilitating how parents may be feeling on that particular day and where one could locate them if they are not at the immediate bedside. Nurses are the first resource when it comes to finding out the clinical status of the infant and whether or not parents would be amenable to discussing research. Having as much knowledge and information at the time of the trial consideration has only been beneficial in obtaining or foregoing consent.

The previously mentioned studies that discussed SES and race with regards to consent rates did so in a way where it was consenting for a "hypothetical trial". There appears to be no clear-cut evidence that race or SES status plays a role in the rates of trial

consent. Parents willing to give consent on behalf of their infant have been wealthy, poor, college educated, and high school dropouts. The same applies for those parents unwilling to give consent. It is difficult to base rates of consent on a hypothetical trial, first and foremost because parents may feel differently when they are actually in the situation where trial consent would be sought. Second, parents had to give consent to take part in the hypothetical trial; therefore parents may possibly be more willing to the idea of research participation. Parents largely act in the best interest of their baby when it comes to research participation. Giving parents the most information at an appropriate level of understanding will only help to facilitate the best decision for themselves and their infant.

Conclusion

Most parents are willing to allow their baby to participate in some sort of clinical trial that takes place in the NICU. Abiding by the following ensures that the clinical care of the baby and the needs of the family are respected.

- The physician needs to take the time to appropriately explain the clinical trial without overwhelming the parents with a plethora of information.
- Have a well-understood picture of the clinical status and course of the neonate before approaching parents for consent.
- Each clinical trial should be reviewed for appropriateness in any given baby and each family should only be approached for one research study in the first 72-hours of their baby's life.
- Should the baby become eligible for subsequent research studies, solicitations for consent should occur a minimum of 48-hours apart.

- Above everything else, the care and consideration for the parents and family comes before any clinical trial.

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