Published in final edited form as:

Nurs Res. 2019 ; 68(2): E11–E20. doi:10.1097/NNR.0000000000000335.

Best Practices for Obtaining Genomic Consent in Pediatric Traumatic Brain Injury Research

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Abstract

Background: Precision health relies on large sample sizes to ensure adequate power, generalizability, and replicability; however, a critical first step to any study is the successful recruitment of participants.

Objectives: This study seeks to explore how the enrollment strategies used in a parent study contributed to the high consent rates, establish current best practices that can be used in future studies, and identify additional factors that contribute to consent into pediatric traumatic brain injury (TBI) biobanks.

Methods: Retrospective secondary analysis of data from a parent study with high consent rates was examined to explore factors affecting consent into biobanking studies.

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Conflict of Interest: The authors do not report any conflict of interest in conducting this study.

Ethical Conduct of Research: All procedures performed in this study were in accordance with the ethical standards approved by the Duke University Institutional Review Board.

Results: Of the seventy-six subjects who were approached, met the eligibility criteria, and reviewed the consent form, only $n = 16$ (21.1%) declined to participate. The consented group ($n = 60$) represents 64.5% of those who met the eligibility criteria upon initial screening ($n = 93$) and 78.9% of those with confirmed eligibility ($n = 76$). Analysis of screening data suggested there were no major barriers to consenting individuals into this pediatric TBI biobank.

Discussion: There were no demographic or research-related characteristics that significantly explained enrollment. Ethically, to obtain true informed consent, parents need to understand only their child's diagnosis, prognosis, and medical care, as well as the purpose of the proposed research, and its risks and benefits. Researchers need to implement best practices, including a comprehensive review of census data to identify eligible participants to approach, a prescreening protocol, and effective consenting process to obtain informed consent so that precision care initiatives can be pursued.

Keywords

brain injuries; children; human genetics; precision health; trauma

Traumatic brain injury (TBI) is the leading cause of death and permanent disability in children with common causes of pediatric TBI including falls, blunt force trauma, and motor vehicle collisions in which the child is a passenger or pedestrian (Wilkinson et al., 2017). Despite the high incidence and increasing rates of TBI and its substantial effect on health outcomes and quality of life, there is no Food and Drug Administration (FDA) approved treatment for TBI in children or adults (Narayan et al., 2002; Stanley et al., 2012). In all age groups, TBI remains understudied and the majority of published human studies to date have enrolled only adults; together, these contribute to significant gaps in the pediatric TBI knowledge base. A review of the limited published evidence found that the majority of pediatric TBI intervention studies enrolled one child or less per month per recruitment site; yet, there is little discussion of how to increase enrollment of TBI participants and no consensus on how to address existing barriers to screening and consenting efforts (Menon & Ward, 2014; Natale, Joseph, Pretzlaff, Silber, & Guerguerian, 2006; Stanley et al., 2017).

A critical first step to any study is the recruitment of participants. The arduous process of enrollment in all TBI studies and particularly in pediatric TBI becomes especially problematic in the context of molecular genomic research. Without recruitment of a sufficient number of participants into sample repositories (biobanks), studies may lack sufficient power to detect statistically significant relationships between biological markers and clinical outcomes, delaying advances in precision health (Reuter-Rice, Eads, Boyce, & Bennett, 2015). Moreover, recruitment of large numbers of cases into biobanks promotes generalizability of findings to the clinical population of interest as well as fuels ongoing discovery by supporting secondary analysis and data sharing. Biobanks are important because evidence suggests that some biomarkers may predict recovery or reflect pathological processes that could be targeted therapeutically (Au & Clark, 2017). Unfortunately, existing data is largely limited to adult studies and the state of the science lags behind for pediatric TBI (Reuter-Rice et al., 2015). Indeed, two recent literature reviews found pediatric-specific evidence was grossly underrepresented with biomarkers in pediatric TBI cases being examined in only 16 of 131 (Reuter-Rice et al., 2015) and 16 of 7,150

(Daoud et al., 2014) publications. Both literature reviews searched multiple databases to identify studies of biomarkers and gene association in pediatric TBI. The review conducted by Daoud et al. (2014) did not limit the search to date of publication and excluded review articles. However, the review conducted by Reuter-Rice et al. (2015) limited the scope to all papers (reviews and data-based) published in the last 10 years focusing on children aged 18 years or younger who were hospitalized. Due to these differences in search criteria, there was little overlap in the articles cited, with only six of the 16 papers included both reviews. Moreover, it is posited that the genetic markers found to be related to recovery in adults may be significantly different in the developing brain (Kurowski, Martin, & Wade, 2012). For these reasons pediatric TBI biobanks will be an essential resource for improving the outcomes of this understudied population. Thus, efforts to maximize the success of screening and consenting processes merit exploration.

Beyond the need for a deeper understanding of pediatric TBI, biobanks represent a valuable resource to the research community. In some clinical populations, such as rare diseases, biobanks represent a truly invaluable research tool that often leads to direct benefit to patients (Lochmüller et al., 2010). Economic benefits of biobanking have also been empirically explored, including reduced clinical trials evaluation costs, contribution to process efficiencies, and improvements in patient diagnosis (Rogers, Carolin, Vaught, & Compton, 2011).

There are several factors that affect successful recruitment into pediatric TBI biobanks. First, personnel must always be available to promptly detect potential patients with TBI by prescreening the hospital census and then further screening the electronic health record (EHR) to confirm inclusion and exclusion criteria are met for a potential participant. Next, personnel must be available to travel to the clinical site and the parent or legal authorized representative (LAR) must be identified, available, and approached. Eligibility should be confirmed and interest solicited before reviewing study paperwork to minimize burden on the family. For interested and eligible individuals, the consent must be reviewed and the parent/LAR must decide whether or not to enroll the child or decline participation. Finally, the child should be evaluated for capacity to assent based on age and current health status, and if he or she is deemed able to provide assent, the child should also be given the opportunity to decline participation or provide informed assent. At each stage of the process, potential participants may be lost. Moreover, many studies have a target window for biospecimen collection—which should be kept as consistent as possible—appreciating that several factors affect the time from injury to sample collection (Reuter-Rice et al., 2015) and taking care to not rush or pressure the potential participant.

Factors that could negatively affect screening efforts include a lack of available study personnel to monitor the hospital census, incomplete records, and inconsistent documentation across providers. Barriers to approaching families include parent(s) or study personnel being unavailable. Even when parents and study staff are available and parent(s) are approached for consent, parents are much more restrictive in their willingness to release their child's biospecimen, as well as associated personal and health data, compared to adults consenting for herself/himself. These lower rates are due to parental concerns of unknown future risks to the child (Burstein, Robinson, Hilsenbeck, McGuire, & Lau, 2014). Further,

many parents do not know what a biobank is, often mistaking it for a “freezer” or “blood donation.” Likewise, many parents mistakenly associate genetic data only with hereditary diseases, and do not understand the potential link of genetic components to TBI recovery (Salvaterra et al., 2014). Beyond these documented misconceptions, very little is known about factors that affect consent/assent into biobanks, except that the most commonly stated reason for participation is the altruistic desire to help others (Kassam-Adams & Newman, 2005; Salvaterra et al., 2014).

Enrollment rates into pediatric TBI studies tend to be low, ranging from 35%–62% (Dennis et al., 2017; Mollayeva, Cassidy, Shapiro, Mollayeva, & Colantonio, 2017; Pearl et al., 2013; Wilkinson et al., 2017). Worse yet, any reporting of recruitment success in pediatric critical illness research is the exception and not the norm; a recent meta-analysis of 215 studies found that 80% of publications did not provide sufficient data to determine what proportion of screened individuals met eligibility criteria, and 77% did not provide sufficient information to determine the recruitment rate (Hudson et al., 2017). Beyond the underreporting of recruitment rates, no pediatric TBI study to date has systematically reported on the reasons for not obtaining consent in eligible individuals, as has been done in other pediatric critical care populations (Menon & Ward, 2014).

Considering the slow progress of pediatric TBI studies, evidence is needed surrounding strategies that research teams can implement to maximize the success of their own recruitment. The primary purpose of this secondary analysis is to use data and study protocols to explore how the enrollment strategies used in the parent study may have contributed to the relatively high consent rates compared to published literature. A secondary aim is to reflect upon these successes to establish current best practices that can be used in future studies. A final aim is to identify additional factors that contribute to consent into pediatric TBI biobanks.

Methods

Parent Study

Following institutional review board (IRB) approval, children with TBI were recruited into the parent study biobank to support analysis of the relationship between biomarkers and clinical outcomes after brain trauma. The recruitment period was between December 2012 and July 2015. Screening and enrollment was a four-step process which was documented to inform future recruitment efforts, including the analysis used in the present daughter study, to create an electronic trail of accessed medical records to verify Health Insurance Portability and Affordability Act (HIPAA) compliance, and to demonstrate respect for the patient and their family by not approaching if death appeared imminent. The four-part process of prescreening the census, screening the patient chart, approaching the patient to confirm eligibility and solicit interest, and reviewing paperwork is depicted in Figure 1 and described below.

First, a prescreen of the patient census on the hospital units of interest was used to identify patients with a chief complaint suggestive of possible TBI (e.g., fall; motor vehicle collision) without evidence of any violation of study inclusion/exclusion criteria (e.g., age,

nonacquired brain injury). Second, the medical records of patients identified as potential candidates in the preliminary scan were examined and screened to further establish eligibility using the study's inclusion criteria (e.g., previously healthy children, aged 10 days to 15 years, admitted for trauma related brain injury with access for biologic sampling and Transcranial Doppler Ultrasound insonation) and exclusion criteria (e.g., history of developmental delay, acquired brain injury). Third, whenever possible, the parent or LAR of a child who appeared eligible upon screening were approached to solicit interest in hearing about the study and confirm eligibility. Fourth, if warranted, review the informed consent document with the parent/LAR. The informed consent and assent documents were provided in English and Spanish, with translation services available as needed. Interested individuals were enrolled into the parent study, the results of which have been previously published (Dienes, Chang & Reuter-Rice, 2018; Reuter-Rice, Regier, Bennett & Laskowitz, 2018; Vaewpanich & Reuter-Rice, 2016). The consent form allowed for the use of the collected samples for the parent study, as well as potential use in future related TBI studies. The parent study has two consent forms, one for the main study and a second consent for the biobanking of samples for future related work. It was stated in the biobank consent form that the samples would be kept until the samples were no longer viable or the parent withdraws the child from the study. Four buccal samples were collected from participants initially. Blood, urine, or cerebrospinal fluid (CSF) samples were collected at Days 1, 2, 3, and/or 5, whenever possible. In addition, the team elected to not approach any family with a child who presented with a devastating brain injury that would warrant a brain death examination within the first 24 hours of admission.

Daughter Study

This study is a retrospective secondary analysis of data from the parent study. SPSS version 25 was used for all data management, cleaning, and analysis. Descriptive statistics were generated separately for two groups of individuals who appeared eligible upon screening: Those who enrolled versus those who were not enrolled due to brain death, inability to approach the parent, or because the parent declined the offer to participate. The percentage of individuals who meet screening eligibility criteria who were enrolled was calculated using the number of individuals whose medical records suggested they were eligible. Formal statistical testing was performed using chi-squared analysis of preliminary data obtained during screening: sex, race, admission unit, and mechanism of injury. Because of the small sample size of eligible individuals and the minimum required cell size of at least $n = 5$ for chi-squared analysis, the following variables were recoded: race (White vs. other), mechanism of injury (fall vs. other), and admission location (intensive care unit [ICU] vs. other).

Data were analyzed separately for individuals confirmed to be eligible who consented versus those who declined. This was done to account for those individuals who seemed eligible upon screening but later found to not meet inclusion/exclusion criteria (e.g., children facing imminent death) and other individuals who could not have their eligibility confirmed due to a failure to make contact with the family. The percentage of individuals confirmed to be eligible who were enrolled was based on only those potential participants whose families were approached and had eligibility confirmed. The duration of the recruitment period was

calculated using the start and end dates provided by the parent study and the recruitment rate was calculated as the number of enrolled individuals divided by recruitment duration. To supplement these analyses, the principal investigator (PI) and clinical research coordinators (CRCs) involved provided insights into factors they thought may have contributed to this study's success, though not all of these ideas could be formally tested due to a lack of available data in accordance with the original human subjects' research approvals and HIPAA guidelines.

Results

As depicted by Figure 2, in the parent study, a total of $n = 203$ individuals were preliminarily screened; upon further screening of the EHR, only $n = 93$ fulfilled the preliminary eligibility criteria. Of the 93, an additional $n = 17$ (18.3%) were not approached for consent due to one of three reasons. First, in five cases, the patients were excluded because they met criteria for brain death or imminent death upon evaluation (5.4%). Eligibility consent could not be obtained in eight patients because a parent/LAR was unavailable (9.0%), or the study personnel was not available to approach the parent ($n = 4$, 4.5%). The remaining 76 who were approached met the eligibility criteria and the consent form reviewed; of those, only $n = 16$ (21.1%) declined to participate resulting in a total sample of $n = 60$. The consented group represents 64.5% of those who met the eligibility criteria upon screening ($n = 93$) and 78.9% of those with confirmed eligibility ($n = 76$).

Analysis of screening data suggested there were no major barriers to consenting individuals into this pediatric TBI biobank. There were no statistically significant differences in demographics, injury mechanism, or admission unit among those children who were eligible upon screening who were subsequently enrolled versus those who were lost or declined to participate (Table 1). When comparing consenting and declining individuals, there were no statistically significant differences in demographics, injury mechanism, or admission unit (Table 1). Additional data was recorded for individuals who consented and enrolled in the parent study (Table 2). Enrolled cases had mild, moderate, and severe injury (i.e., a score on the Glasgow Coma Scale [GCS] of 3–15) and ranged in age from 10 days to 15 years. Consent was most commonly obtained from the mother (70.0%); in only one case (1.7%), consent was obtained from a LAR instead of a parent. For $n = 59$ cases (98.33%), assent could not be given by the child directly, as he or she was either too young ($n = 49$; 64.5%) or too acutely impaired by injury to do so ($n = 26$; 34.2%). Among the enrolled individuals 13.3% identified as Hispanic/Latino; no ethnicity data was collected for screened/approached individuals.

Discussion

Relationship to Past Literature

The current study is unique in that it is the first to empirically evaluate factors associated with successful enrollment of pediatric TBI cases into a biobank. There were no demographic or research-related characteristics that significantly explained enrollment. Enrollment rates in the parent study were high compared to other publications, with 60 children consented out of the 76 children approached (78.9%). The remaining 17 children

were not contacted due to variables such as brain death, lost due to lack of study personnel, or unavailability of the parent/LAR. These enrollment percentages were higher than those previously published (35%–62%); notably, each study varied in their calculation of the enrollment rate (Dennis et al., 2017; Mollayeva et al., 2017; Pearl et al., 2013; Wilkinson et al., 2017). For example, Mollayeva et al. (2017) reported their enrollment rate prior to confirming eligibility; upon reviewing eligibility criteria additional participants were excluded, altering their originally reported enrollment rate of 61.8% to 52.8%. Likewise, Dennis et al. (2017) reported participation rates of 35%; however, the reported rate included ineligible patients.

The parent study's recruitment rate of 1.94 participants per month was higher than what has been found in the majority of past studies, reviewed by Natale et al. (2006). Only one past study demonstrated higher rates than 1 per month per site; however, this study was characterized by unique inclusion criteria that may have contributed to the high rates (Gausche et al., 2000). Specific factors in the parent study believed to have contributed to these relatively high enrollment rates include a high availability of the PI and CRCs to approach the parent/LAR of a potential participant and effective communication between team members when a potential participant was identified whose parent was unavailable so that follow-up could be pursued, as well as the prescreening protocol. The prescreening protocol streamlined the process by minimizing the time spent approaching ineligible cases (Figure 3). Moreover, time spent with the potential participants was more efficient because a thorough prescreening of the census and screening of the charts meant the study personnel could be prepared to ask individualized questions. Another factor enhancing effective communication included the availability of both English- and Spanish-speaking consenters and resources. Combined, these efforts led to only four (4.3%) out of the 93 individuals deemed eligible upon screening being missed by study personnel. Beyond study team availability, parent inaccessibility is a barrier to recruitment; in this study, there were eight potentially eligible cases (8.6%) where the child's parent(s) were not available during the study eligibility window and were subsequently lost to follow-up. Of those eight potentially eligible children, five of them had parents who were hospitalized for injuries sustained at the same time as the child but who were referred to other hospitals.

Contributing factors to parent/LAR unavailability likely have multifaceted roots which could not be explored using data from the parent study. However, scenarios that explain the unavailability of parents/LAR include, injured parents being treated in different healthcare facilities (e.g., both the parent and child were in the same motor vehicle collision), parents who had to care for other children, or lack of transportation to the hospital. Past studies corroborated parent/LAR unavailability was a barrier to informed consent due to the asynchronous timings of patient and guardian arrival (Stanley et al., 2017). These factors are challenging to study due to the necessary privacy safeguards that protect the personal information of individuals who do not consent to participate in a study. Notably in the data, seven of the eight participants whose parent or LAR could not be approached were non-White. Unfortunately, this study was underpowered to statistically test for group differences based on race/ethnicity. This represents an important area for follow-up in future studies.

There were no significant differences in the sex or race of the individuals whose EHR were screened but not consented (declined, excluded due to brain death, or lost due to lack of study personnel, or unavailability of a parent/LAR) versus consented and enrolled. Yet, there was a trend toward individuals who were screened but not enrolled being non-White ($p = .074$). Notably, considering there was no significant difference in the race of those who declined versus enrolled ($p = .602$), this was not due to a difference in interest between groups, but rather a tendency for more non-White families to not be approached due to brain death, a lack of study personnel, or unavailability of the parent/LAR. Unfortunately, this trend could not be formally explored using the existing data, since the small sample size in this study was underpowered to detect such differences. The cell sizes for chi-squared analysis were < 5 ; in total only 17 individuals were lost, with four being missed due to lack of personnel, five excluded for brain death, and eight lacking a parent/LAR to approach. This should be examined in future studies to add to the sparse literature on how race and ethnicity affect enrollment (Daunt, 2003; Halbert, McDonald, Vadaparampil, Rice, & Jefferson, 2016). Although additional data is needed, this preliminary data suggests that the parent study sample may be generalizable to the patient population at the health center where recruitment occurred in terms of demographic characteristics. This data also proposes that there was no specific barrier to enrolling certain racial or ethnic groups once a family was approached, which, had they been evident, may have pointed to an issue in translation of consent forms or available translation services.

Challenges and Approaches to Enrollment

Ethically, many factors need to be considered—especially in observational studies not offering potential benefits—such as the parent study and most other studies involving biobanking. When approaching families for enrollment, in order to obtain true informed consent, parents/LAR need to understand not only their child's pre-injury health, injury diagnosis, prognosis, and medical care, but also the purpose of the proposed research, as well as its risks and benefits (Natale et al., 2006). A major obstacle of obtaining true consent is explaining the nature of the research to parents (Barfield & Church, 2005). Prior studies suggest that not only do parents overestimate their understanding of the informed-consent discussion, but only half of participants understand the aim of the study (Anderson, Newman, & Matthews, 2017). When participants have been asked to recall the aim of the study in which they participated, they were frequently unable to do so; rather, they remembered what they did for the research team, such as give a blood or urine sample, answer questions, etc. (Anderson et al., 2017). Further, with biobanking, researchers need must take into consideration new ethical questions that have surfaced. A common misconception by participants is that they will receive a therapeutic treatment. Researchers need to be clear that by participating in biobank research, it is only observational; the benefit will be for greater knowledge of diseases to help future patients (Anderson et al., 2017; Bernhardt et al., 2015). Another obstacle to consenting in biobanking studies is participant fear and hesitancy, due to mistrust that their data will be shared with third parties without their knowledge and used for purposes other than what they consented to (Kraft et al., 2018). The need for an open, trusting relationship between researchers and participants is crucial to ensure truly informed consent (Kraft et al., 2018). In the parent study, the use of clear and

detailed consent forms and review of these documents by trained personnel helped to address these barriers (Figure 3).

Another ethical challenge is the rights of children enrolled in the study. The value of involving children and adolescents in their own medical decision-making is increasingly being recognized (Giesbertz, Bredenoord, & van Delden, 2015; Katz & Webb, 2016). Despite this, there is evidence that most children younger than 9 years of age lack the capacity for participation in clinical trials, and there is no definitive low age cutoff for ability to provide assent (Barfield & Church, 2005; Giesbertz et al., 2015; Leibson & Koren, 2015). In TBI cases, children may also be incapacitated or mentally debilitated and unable to state their desires, regardless of age or maturity status. In the parent study, assent was often not attained due to a low GCS score or symptoms of TBI. In pediatric research, efforts should be made to maintain the best interests of the child (Barfield & Church, 2005), especially considering that children's autonomy depends upon age and whether or not they are developmentally advanced enough to provide assent for research. Moreover, in nontherapeutic studies, such as collecting DNA for biobanks, a balance between potential harm to child during research and the critical need for advancements in pediatric TBI research and clinical management must be achieved (Barfield & Church, 2005; Giesbertz et al., 2015). The appropriate transfer of information to guardians and the children—in particular, the potential risks and benefits—is at the heart of consent (Leibson & Koren, 2015). In an ideal case, the researcher would be able to obtain assent of the child and parental consent while maintaining an overriding aim of attending to the best interests of the child (Barfield & Church, 2005).

Key Roles in the Parent Study

Principal Investigator (PI).—The PI is ultimately responsible for the planning and execution of the research study. Starting with the initial study conceptualization and drafting of IRB documents, the PI's efforts are key to the study's success. Past publications have discussed the effect of writing consent forms consistent with best practices (Dove, Avar, Black, & Knoppers, 2013). Moreover, in the parent study, the PI selected all CRCs and ensured they were adequately trained. The PI was on call 24/7 to answer any questions or approach families who met screening criteria. The PI's clinical expertise in the pediatric population as a pediatric acute care nurse practitioner and Fellow of the American College of Critical Care Medicine, as well as recognition as a nurse researcher with numerous publications in the field of pediatric TBI also contributed to the success of the study.

Clinical Research Coordinator (CRC).—Supporting the PI in this study were five CRCs over a three-year timeframe; each CRC was experienced in their role and comfortable interacting with pediatric patients and their families. They were knowledgeable about the study goals, and had a folder containing key information needed to screen and enroll participants (e.g., checklist, information on how to request translation services, directions for how to navigate the EHR). Each CRC was trained to be proficient in all aspects of the study protocol including screening, consenting, and collection of data and biosamples; adequate training resulted in improved consistency and therefore consent rates. The CRCs built rapport with the families by maintaining contact with them every day of hospitalization

during the study period. Along with actively pursuing new, potential participants and following up with enrolled participants, the CRCs developed a thorough prescreening process which minimized access to and use of protected health information. With the use of this process, detailed above, the EHR of only a few patients who did not meet eligibility criteria were accessed.

Registered Nurses (RNs).—RNs as study champions. In this study, five nurses self-selected as study champions over the three-year timeframe. They were involved in multiple aspects of the study. These RNs were not only experienced and comfortable on their units but also passionate about pediatric TBI. They alerted the study team of potential patients, as well as assisted newer RNs with data-collection procedures on enrolled individuals. These nurses were acknowledged by the PI in formal letters to the director of nursing, and their study participation counted towards their clinical ladder criteria, promoting future involvement in similar ventures. The role of nurses in enrollment remains understudied and represents an avenue for future research, since emerging evidence does suggest nurses play important roles in facilitating clinical research (Axson, Giordano, Hermann, & Ulrich, 2017; Susilo, van Dalen, Chenault, & Scherpbier, 2014; Tinkler, Smith, Yiannakou, & Robinson, 2018).

Parents and Legal Authorized Representatives (LARs).—While not a formal member of the research team, parents/LARs constitute key players in biobanking enrollment. This participation is especially laudable considering consent is heavily burdened by emotion; TBI is shocking and distressing, creating a challenging environment for good, informed decision-making. For parents, receiving news of life-threatening conditions in their children create emotional and psychological stress that can interfere with decision-making (Katz & Webb, 2016). Parents tend to be both emotionally and cognitively overwhelmed, especially in the initial hours and days when recruitment to a study would occur (Natale et al., 2006), which may contribute to low enrollment rates. In a prior study on pediatric research in a critical care population, the most commonly stated reason for parental consent refusal was being overwhelmed, and the second most common being they did not want any unnecessary procedures performed (Menon & Ward, 2014). Notably, 70% of the family members who signed the consent for study participation were the participant's mother.

Despite these stressors, the parent study found parents/LARs expressed a strong desire to help other children via participation in the study. This is consistent with a prior study which found that 52% of children and 74% of parents were glad they participated in the study, and that primarily both parents and children felt good about helping others, 90% and 77%, respectively (Kassam-Adams & Newman, 2005). The beneficence and willingness of the parent(s)/LAR(s) to participate likely contributed greatly to the success of the parent study.

Limitations and Future Research

Although this study makes important contributions to the knowledge base, it is limited in that it was conducted at a single medical center, restricting the study sample size and generalizability to the entire population of TBI cases. Future studies should be expanded to multiple recruitment sites to ensure a greater pool of potential candidates. The need for

multisite studies and screening at nonpediatric hospitals are cited in the literature; these strategies require significant effort but could greatly improve enrollment rates. A previous study reported that a majority of children with severe TBI were discharged from either a children's hospital (41%) or a children's unit in a general hospital (34%), indicating that studies will need to diverge from focusing on pediatric-specific hospitals, and begin multicenter studies to obtain more data (Natale et al., 2006, Stanley et al., 2012). The study was unable to follow-up with those who declined to enroll. In follow-up work, it is worth further exploring factors that affect recruitment that were not measured in this study, such as parent level of education, literacy level, or socioeconomic status. Future studies should also seek IRB approval to survey those who decline to enroll to collect data on how to improve the consenting process and motivations for declining participation.

Conclusion

The goal of this inquiry is to promote the enrollment of more pediatric TBI patients into biobanks and to garner evidence to support precision-care initiatives. Based on these preliminary findings, the importance of thorough screening and availability of the PI and CRC is not to be undervalued, nor is the role of having support from nurses and nurse study champions. Ensuring research staff are not the limiting factor is crucial, since some barriers to enrollment are beyond the researchers' control, such as the unavailability of parents. There are many reasons parents who are approached would choose not to participate in research, including privacy concerns, religious reasons, or perceived participant burden. It is up to the research team to design and execute the study in such a way that minimizes loss of participants.

In order for pediatric TBI research to advance, researchers need to be efficient in using census data to identify eligible participants to approach. Implementing a prescreening protocol, such as in the parent study, may expedite the process and avoid HIPAA compliance issues. Then, once eligible individuals are identified, researchers must be successful in obtaining informed consent from the parent and, if possible, assent from the child. Finally, efforts must be made to retain participants in the study so that they are not lost to lack of follow-up or ask to be withdrawn from the study/biobank. Considering the relatively low incidence of TBI among children and the propensity for rapid discharge shortly after pediatric TBI, these best practices can potentially make a substantial difference in recruiting and biobanking efforts; a critical first step in advancing the state-of-the-science in pediatric TBI.

Acknowledgments:

Research reported in this publication was supported by the National Institutes of Health, the Adaptive Leadership for Cognitive Affective Symptom Science ADAPT Institute of Nursing Research Center of Excellence under Award Number NINR 1P30 NR014139-01, and The Robert Wood Johnson Foundation Nurse Faculty Scholar under Award Number 71244. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We would like to thank Registered Nurse Champions Ron Ryen, Erin McCallum, Martina Watkins and Jared Leonard for their dedication to the this research study.

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Figure 1.

Diagram outlining the four-step recruitment process: prescreening the census, screening the patient chart, approaching the family to confirm eligibility and solicit interest, and reviewing paperwork.

Figure 2.

Flowchart of Participants in this Study. The flow of the $N=203$ individuals screened individuals to the $N=60$ individuals enrolled is explained in this figure with the reasons for participant loss described.

Figure 3.

Action Items to Be Considered by Other Research Teams. Here we outline five strengths of the parent study's recruitment strategy that could be adapted for use in studying by other investigators.

Table 1

Comparison of Families Screened and Approached but Not Enrolled to Those Who Consented and Enrolled.

Characteristic of Enrolled Participants		Screened and Eligible but Not Enrolled		Approached but Not Enrolled	
Characteristic	Enrolled (n=60)	Not Enrolled (n = 16)	χ^2 (p-value)	Not Enrolled (n = 16)	χ^2 (p-value)
Race (White): N (%)	37 (61.7%)	14 (42.4%)	3.183 (.074)	11 (68.8%)	0.272 (.602)
Sex (Male): N (%)	34 (56.7%)	22 (66.7%)	0.889 (.346)	11 (68.8%)	0.764 (.382)
Admission (ICU): N (%)	40 (66.7%)	18 (54.5%)	1.333 (.248)	7 (43.8%)	2.811 (.094)
Mechanism (Fall): N (%)	23 (38.3%)	13 (39.4%)	0.010 (.920)	9 (56.3%)	1.663 (.197)

Table 2

Additional Participant Characteristics and Research-Related Characteristics for the Consented Sample (n=60).

Research-Related Characteristics of Consented Individuals		
Team Member who obtained consent, (<i>n</i>) %	CRC 1	(22) 36.7%
	CRC 2	(20) 33.3%
	PI	(8) 13.3%
	CRC 3	(8) 13.3%
	CRC 4	(1) 1.7%
	CRC 5	(1) 1.7%
Family member who signed consent, (<i>n</i>) %	Mother	(42) 70.0%
	Father	(17) 28.3%
	Guardian	(1) 1.7%
Assent Obtained, (<i>n</i>) %	Yes	(1) 1.7%
	No	(59) 98.3%
Additional Demographics on Consented Individuals		
Ethnicity, (<i>n</i>) %	Non-Hispanic or Latino	(52) 86.7%
	Hispanic or Latino	(8) 13.3%
Glasgow Coma Scale Severity, (<i>n</i>) %	Mild	(44) 73.3%
	Moderate	(2) 3.3%
	Severe	(14) 23.3%
Age in years, mean (minimum-maximum, standard deviation [<i>SD</i>])	5.5 years (0 – 15; 5.45)	
Length of stay in days, mean (minimum-maximum, standard deviation [<i>SD</i>])	9.52 days (1 – 81; 15.82)	
Hours to consent from admission to hospital, mean (minimum-maximum, standard deviation [<i>SD</i>])	16.44 hours (4 – 43; 8.65)	