Parent Provider Alliance (PPA) CPCCRN Protocol Number 075

Collaborative Pediatric Critical Care Research Network
Eunice Kennedy Shriver National Institute for Child Health and Human Development (NICHD)

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PROTOCOL TITLE:

Parent Provider Alliance

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I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated. I confirm that if I or any of my staff are members of the Institutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

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Contents

Abstract

About 55,000 children die annually in the U.S. affecting the health and welfare of many families. Most of these deaths occur in hospitals, mainly in intensive care units. Parents whose children die in pediatric intensive care units (PICUs) are at high risk for adverse health outcomes. The Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN) previously demonstrated a high prevalence of complicated grief, a chronic debilitating disorder, among parents whose children died in PICUs.[1, 2] Therapeutic alliance, a key component of patient and family-centered care (PFCC),[3] is the collaborative bond that develops between patients/families and their healthcare providers. The strength of therapeutic alliance has been shown to affect treatment outcomes for many conditions. Therapeutic alliance includes high quality communication, caring and trust, aspects of healthcare deemed essential by parents of terminally ill children. What is not known is the extent to which therapeutic alliance can reduce complicated grief and other adverse health outcomes among parents after a childs death in a PICU.

1 Study Summary

1.1 Hypotheses

The hypotheses of this study are:

1. The extent of therapeutic alliance reported by parents is influenced, in part, by parent and child attributes, and by characteristics of the childs clinical course.
2. Greater therapeutic alliance will be associated with reduced complicated grief, depression, post-traumatic stress and poor physical health, and increased post-traumatic growth among parents 6 and 13 months after their child's death.

1.2 Specific Aims

This project has the following Specific Aims:

Specific Aim 1. Determine the extent of therapeutic alliance bereaved parents perceive to have occurred between parents, and their child's physicians and other healthcare providers during the child's PICU stay.

Specific Aim 2. Determine the extent to which therapeutic alliance is associated with parents' health outcomes after their child's death in a PICU.

1.3 Subject Eligibility, Accrual and Study Duration

Eligible participants will be identified by on-site study staff. Inclusion criteria are:

1. Child of the parents died in a CPCCRN ICU
2. At least one of the parents is the biological mother/father or the legal guardian of the deceased child
3. At least one of the parents or legal guardians speaks English or Spanish
4. The parent(s) and/or legal guardian(s) are at least 18 years of age

2 Rationale

Parents of children who die in PICUs are at high risk for adverse health outcomes, yet the impact of therapeutic alliance on bereaved parents' health is unknown. The CPCCRN Bereavement Project has identified high rates of complicated grief among bereaved parents in PICUs, and factors associated with complicated grief such as parent attachment styles.[1, 2] However, knowledge of modifiable factors such as therapeutic alliance that could potentially improve bereaved parents' health is needed.

The proposed research would be beneficial to the field of critical care medicine for the following reasons:

- It would be the first study to examine therapeutic alliance in PICUs, and the first to specifically investigate the role of therapeutic alliance on bereaved parents' health after their child's death in a PICU.
- In addition to the parent-physician relationship, therapeutic alliance between parents and PICU staff will also be evaluated.

Greater understanding of therapeutic alliance in PICUs will open new avenues for improving pediatric end-of-life care and the support provided to bereaved parents and families.

3 Background

Parental grief after a child's death is more intense and prolonged than grief suffered by adults after the death of a spouse, parent or sibling.[4–6] Nearly all studies examining mental health among bereaved parents report high risk for disorders such as complicated

grief,[1, 2, 7, 8]depression,[9] and post-traumatic stress.[10] Among parents whose children die in PICUs, 60% have symptoms consistent with complicated grief 6 months after the death, which persist in 40% at 18 months.[1, 2] Bereaved parents have higher risk of first time psychiatric hospitalization and suicide than non-bereaved parents.[11–14] Many studies report higher rates of physical illness among bereaved parents.[15–18] Despite these risks, little is known about the role PICU physicians and staff may play in bereaved parents' ability to adjust to their childs death.

Therapeutic alliance was first described in the psychotherapy literature as an empathic bond between patient and therapist, and is highly regarded as an essential psychotherapeutic agent in the prediction of treatment response. It is is a multifaceted construct reflecting the strength and quality of relationship between a patient/family and their physician; elements include mutual feelings of trust, caring, respect, collaboration, and understanding.[3] In previous studies it has been shown to have positive effects on health outcomes in adults with diabetes,[19] HIV[20] and bulimia nervosa,[21] and in children with cancer,[22] obsessive compulsive disorder,[23] and arthritis.[24] Therapeutic alliance has not been thoroughly investigated during pediatric critical illness despite its demonstrated benefits in other serious conditions. In the PICU, research suggests that therapeutic alliance extends beyond the patient/family-physician relationship to include relationships patients and families have with other healthcare providers (e.g., nurses).[25, 26] Families facing medical crises in PICUs rely heavily on a select support network, and healthcare providers with whom they are recently acquainted are drawn quickly into their inner circle of support.[27]

4 Study Design and Procedures

4.1 Study Design Overview

The study will be based around a multisite longitudinal survey of parents 6 & 13 months after their child's death in a CPCCRN-affiliated ICU. Parent characteristics and perceived therapeutic alliance will be assessed at 6 months, while parent health outcomes will be measured at 6 & 13 months.

4.2 Subject Accrual and Study Duration

Medical records of deceased children will be reviewed to obtain child characteristics and details of the clinical course. Based on our study design, we will need to enroll at least 90 families, with at least 1 parent or family member participating. To be able to get such

numbers, we will be attempting to contact 500 families to meet the recruitment goal. The study is anticipated to complete recruitment in a period of 18 months.

4.3 Inclusion & Exclusion Criteria

Inclusion criteria are:

1. Child of the parents died in a CPCCRN ICU
2. At least one of the parents is the biological mother/father or the legal guardian of the deceased child
3. At least one of the parents or legal guardians speaks English or Spanish
4. The parent(s) and/or legal guardian(s) are at least 18 years of age

There are no exclusion criteria for this study.

4.4 Enrollment, Follow Up & Withdrawal

Parents will be mailed an introduction letter that expresses condolences, a research information sheet that explains the study, in addition to two identical sets of surveys (one for each parent, if applicable) 6 months after their child's death. Parents will be asked to complete the surveys and will be given the option of returning surveys by mail, or completing them by telephone. An opt-out phone number (for non-participants) and stamped return envelope (for participants) will be provided with the 6 month survey packets. If no opt-out call or completed surveys are received from parents within one month, parents will be contacted by phone to discuss study participation, and options for completing surveys will again be provided. Parents that complete surveys at 6 months will receive a second set of surveys for completion at 13 months, as explained in the research information sheet. A thank-you note and $25 gift card will be sent to each parent completing surveys at each time point. Consent is implied for parents who return surveys by mail or electronically. Verbal consent will be obtained from parents who complete the surveys by telephone.

5 Study Data Collection

The following clinical data will be collected from the subjects' medical record: name, date of birth, gender, date of death, hospital admission & discharge dates and finally ICU admission dates. The primary diagnoses, along with the cause & mode of death will also be collected.

In the survey participants will be asked their gender, date of birth, race, ethnicity, level of education, marital status, relationship to the deceased subject and finally number of children the participant has.

6 Data Analysis

The hypotheses of this study are:

1. The extent of therapeutic alliance reported by parents is influenced, in part, by parent and child attributes, and by characteristics of the childs clinical course.
2. Greater therapeutic alliance will be associated with reduced complicated grief, depression, post-traumatic stress and poor physical health, and increased post-traumatic growth among parents 6 and 13 months after their child's death.

To evaluate non-response bias, we will compare survey responders and non-responders based on parent and child characteristics. For all responders, we will summarize all variables using mean ± SD (or median, IQR) for continuous variables, and count and percentage for categorical variables.

6.1 Specific Aim Analyses

Specific Aim 1. Determine the extent of therapeutic alliance bereaved parents perceive to have occurred between parents, and their child's physicians and other healthcare providers during the child's PICU stay.

For aim 1, we will assess whether therapeutic alliance differs according to parent and child characteristics based on information obtained from the 6 months survey (specifically the 16 questions built from The Human Connections Scale)[3] This will be done using mixed effects models to account for correlated data between parents in the same family. If there are a substantial proportion of cases with only one parent responder, we will also analyze all associations for mothers and fathers separately. These analyses will be carried out using independent sample t-tests, one way ANOVA, Pearson correlations, and chi-squared tests. If the normality or equality of group variances assumptions are not met for any of the tests, we will use the appropriate non-parametric analog (Wilcoxon rank sum tests, Kruskal-Wallis tests, Spearman correlations). We will use the Tukey correction for multiplicity for all tests involving three or more categories. Two-sided p-values <0.05 will be considered statistically significant.

Specific Aim 2. Determine the extent to which therapeutic alliance is associated with parents' health outcomes after their child's death in a PICU.

For this aim, we will examine the association between parents' health outcomes at 6 months and therapeutic alliance using mixed effects models if there are a sufficient number of cases with responses from both parents; otherwise we will perform ordinary least squares regression for mothers and fathers separately. In terms of outcomes, primary outcomes will be measured by assessing complicated grief symptoms, while secondary outcomes will be measured by assessing depression symptoms, post-traumatic stress disorder symptoms, post-traumatic growth and parents perceived physical health. To adjust for attachment, and other parent and child characteristics, we will use multivariable models, with all variables (except our primary and secondary health outcomes) initially considered for inclusion in the model. We will also consider interaction effects between therapeutic alliance and attachment and between therapeutic alliance and parent characteristics to allow for potential moderation effects. Variables will be included in the model based on stepwise variable selection, with an entry criterion of $p<0.2$ and an exit criterion of $p>0.1$. If multicollinearity is present among any of the predictor variables, we will run separate models for the variables in question and report the better model based on Akaikes Information Criterion (AIC) values. We will follow a similar process for analysis of health outcomes at 13 months. To evaluate factors related to improvement in health outcomes, we will use a binomial mixed effects model, adjusting for health outcomes at 6 months. As a sensitivity analysis, we will use multilevel mixed effects models for all analyses in aims 1 and 2 in order to assess whether site-level characteristics influence the results, and to control for site-to-site variability if needed.

6.2 Sample Size Calculations and Statistical Power

Using the rule of thumb of 10 subjects/variable for multivariable analyses, a sample size of 90 families (with at least 1 parent/family participating) will allow us to include 9 variables in the final models of interest. Moreover, 90 families will provide 90% power to test that a Pearson correlation between two continuous factors is >0.2, if the true correlation is at least 0.5. Based on our prior experience recruiting bereaved parents several months after their childs final hospitalization, we expect about 50% will be unable to be located. Among those located, we expect 50% initial participation and 20% loss to follow-up. Thus, we need to attempt contact with 500 families to meet the recruitment goal.

7 Data Management

7.1 CPCCRN Data Coordinating Center (Utah)

In addition to locally secured, identifiable information, partially identifiable information for all sites will be maintained at the CPCCRN Data Coordinating Center, located at the University of Utah in Salt Lake City, Utah.

7.1.1 Facility, Hardware, Storage, Data Backup and System Availability

The Data Coordinating Center (DCC) in the Department of Pediatrics at the University of Utah School of Medicine provides data coordination and management services for a variety of national research networks. Anchoring these services is a new state-of-the-art, energy efficient data center completed in 2013. The data center facility supports more than 1200 users around the world and provides a secure, reliable, enterprise-wide infrastructure for delivering critical DCC systems and services. The new data center was built using high industry standards and energy efficient cooling solutions. The data center is cooled by Rittal's LCP inline cooling technology, providing efficiency, redundancy and modularity. Cooling is based upon a hot/cold aisle design that allows for even air distribution with minimal hot spots. The data center electrical power system contains a redundant Mitsubishi uninterruptible power system (UPS) with a diesel backup generator. The data center is protected with a FM200 fire suppression system, early warning smoke detectors and a heat detection warning system to act as a secondary system to the smoke detectors. Security guards are on-site conducting access control and rounds 24/7/365. Entry into the data center is restricted by card access and layered security measures and controls. The data center and external building access points are monitored with video surveillance.

In 2011 the data center began a large scale VMware server virtualization deployment. Currently, the data center has virtualized about 95% of its environment. The virtual environment consists of more than 160 virtual servers and nearly 20 physical servers. The data center's virtualization solution provides key advantages:

- high availability – in the event of hardware failure, virtual servers automatically go back online in a seamless process.
- flexible infrastructure – disk storage, memory and processor capacity can be increased or reallocated at any time.
- rapid deployment – servers can be provisioned on-demand with minimal waiting on hardware of software.

The data center also enhanced its storage resources by implementing a networked storage system to support its virtualized environment. The data center currently manages over 50 terabytes of data. The storage solution consists of Dell's EqualLogic PS Series Storage system for providing a virtualized storage area network (SAN). Some of the benefits that are realized through this technology are:

- storage architecture will no longer be a bottleneck for IT services;
- performance is better than with the previous architecture;
- tiered storage is now possible;
- provisioning and reclamation of SAN disk will be much easier; and most important,
- the new architecture includes a redesign of the SAN fabric to include complete redundancy.

Production servers running critical applications are clustered and configured for failover events. Servers are backed up with encryption through a dedicated backup server that connects across an internal 10 gigabit network to a tape drive. Our storage area networking (SAN) applications, clusters, and switch-to-switch links are also on a 10 gigabit network. Incremental backups occur hourly Monday through Friday from 6 am to 6 pm. Incremental backups also are performed each night with full system backups occurring every Friday. Tapes are stored in a fireproof safe inside the data center facility, and full backups are taken off site on a weekly basis to an off-site commercial storage facility.

In the event of catastrophic failure, such as a fire in the server facility, daily backups would probably survive because of the fire suppression system and fireproof safe, but there would be obvious delay in re-establishing data center function because the servers will not survive such a disaster. Total destruction of the data center facility could cause the loss of up to one week's data. In future investments, the data center is making co-location, disaster recovery and business continuity solutions a top priority.

Our information systems are available 24 hours a day, 7 days a week to all users unless a scheduled maintenance interruption is required. If this occurs, we notify all users of the relevant systems, and data entry can be deferred until after the interruption is over. Critical systems availability has exceeded 99.9% for the past two years, and there has been no unscheduled downtime in over five years.

7.1.2 Security, Support, Encryption and Confidentiality

The data center coordinates the network infrastructure and security with the Health Sciences Campus (HSC) information systems at the University of Utah. This provides us with effective firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. Network equipment includes four high-speed switches. User authentication is centralized with two Windows 2008 domain servers. Communication over public networks is encrypted with virtual point-to-point sessions using secure socket layer (SSL) or virtual private network (VPN) technologies, both of which provide at least 128 bit encryption. All of our Web-based systems use the SSL protocol to transmit data securely over the Internet. Direct access to data center machines is only available while physically located inside our offices, or via a VPN client.

All network traffic is monitored for intrusion attempts, security scans are regularly run against our servers, and our IT staff is notified of intrusion alerts. Security is maintained with Windows 2008 user/group domain-level security. Users are required to change their passwords every 90 days, and workstations time out after 5 minutes of inactivity. All files are protected at group and user levels; database security is handled in a similar manner with group-level access to databases, tables, and views in Microsoft SQL Server. Finally, all laptop computers in use in the DCC or in the Department of Pediatrics are whole-disk encrypted.

The data center uses control center tools to continuously monitor systems and failure alerts. Environmental and network systems are also monitored to ensure up time. Highly trained system administrators on staff are available to respond in high risk emergency events.

The investigators and staff of the Data Coordinating Center are fully committed to the security and confidentiality of all data collected for CPCCRN studies. All Data Coordinating Center personnel at the University of Utah have signed confidentiality agreements concerning all data encountered in the center. Violation of these agreements may result in termination from employment at the University of Utah. In addition, all personnel involved with data coordinating center data systems have received Human Subjects Protection and HIPAA education.

The staff, reviewers and investigators involved with this study will be required to sign agreements from the Data Coordinating Center that relate to maintenance of passwords, information system security, and data confidentiality.

7.2 Data Quality Management and Monitoring

The Data Coordinating Center monitors CPCCRN studies on behalf of the investigators and the funding agency. The purposes of monitoring include demonstration of adherence to human subjects protection requirements and assurance of high quality study data. Monitoring is usually done remotely and may also involve physical site monitoring visits. Site monitoring is described in more detail in Section 9.2.

7.3 Record Access

The medical record and study files (including informed consent, and permission) must be made available to authorized representatives of the Data Coordinating Center, upon request, for source verification of study documentation. In addition, medical information and data generated by this study must be available for inspection upon request by representatives of the the National Institutes of Health, Food and Drug Administration, and the Institutional Review Board (IRB) for each study site.

8 Protection of Human Subjects

8.1 Institutional Review Board (IRB) Approval

The Data Coordinating Center and each clinical center must obtain approval from their respective IRB prior to participating in the study. This approval may be accomplished via a central IRB mechanism if this is available within the Network. The Data Coordinating Center will track IRB approval status at all participating centers and will not permit subject enrollment without documentation of initial IRB approval and maintenance of that approval throughout subsequent years of the project.

8.2 Informed Consent

The parent or legal guardian will be informed about the objectives of the study, the benefits and the potential risks in the Research Information Sheet mailed out to them in the 6 month survey packets. They will be given the option of opting out by calling a number. Completing the 6 month survey and mailing it back in or completing the survey over the telephone implies consent to take part in the study.

8.3 Potential Risks

This is a longitudinal study and the research presents no more than minimal risk of harm to subjects and involves no procedures with potential risks.

8.3.1 Loss of Confidentiality

There is risk of loss of confidentiality for data collected in this study. This risk is minimal as each subject will be assigned a unique identifier by the electronic data capture (EDC) system. It will only be possible for the Clinical Center to map this identifier to the subject's medical record number. No direct subject identifiers will be captured by the EDC or stored at the DCC. Staff at the DCC will not be able to determine the identity of any subject enrolled in this study.

8.4 Protections Against Potential Risks

Loss of confidentiality will be mitigated by the use of the CPCCRN Data Coordinating Center which has a highly secure IT infrastructure, and by the existence of trained research staff at participating sites. Data security is described in Section 7.

8.5 Potential Benefits

It is the goal of this research to determine the extent to which therapeutic alliance between parents and healthcare providers in the PICU is associated with bereaved parents' health outcomes. Once the impact of therapeutic alliance on bereaved parents' health is better understood, interventions to promote therapeutic alliance in PICUs can be developed and tested. Such measures will be implemented in PICUs to improve outcomes for bereaved parents.

Participants will be mailed a $ 25 gift card for each survey they complete at each of the 6 month and 13 month time points.

9 Study Training & Monitoring

9.1 Study Training

A formal training program for investigators and research staff will be held prior to the start of enrollment at the Steering Committee Meeting. The training program will cover regulatory topics and Good Clinical Practice. The training will also provide in depth

explanations regarding study procedures, clinical care, data entry procedures, quality assurance, site monitoring, and the informed consent process. A manual of operations will be provided to each investigator prior to the start of enrollment. The manual will detail specific information about the study procedures,and other necessary information. Updates and revisions to the manual will be made available electronically. The Data Coordinating Center, in collaboration with the study investigators (Dr. Suttle) and (Dr. Meert), will be the main contact for study questions.

9.2 Study Monitoring

This study will rely on remote monitoring involving detailed review of the data entered by the Clinical Center and consultations with the Clinical Center investigator and/or research coordinator to review data quality. This may require uploading de-identified copies of specific parts of the medical record, patient study file, regulatory documentation, or other source documents to the Data Coordinating Center staff, who review those materials against the data recorded in the electronic data capture system. This helps assure protocol compliance and accurate data collection. The Data Coordinating Center may conduct remote monitoring activities early in the study to assure protocol compliance and identify any training issues that may exist. For remote monitoring, the documents will be retained in accordance with federal requirements.

10 Regulatory Issues

10.1 Health Insurance Portability and Accountability Act

Data elements collected include the date of birth, date of admission and date of hospital discharge. Prior to statistical analyses, dates will be used to calculate patient age at the time of the study events. The final data sets (used for study analyses and archived at the end of the study) will be de–identified, and will exclude these specific dates.

Data elements for race, ethnicity, and gender are also being collected. These demographic data are required for federal reporting purposes to delineate subject accrual by race, ethnicity, and gender.

For purposes of the DCC handling potential protected health information (PHI) and producing the de–identified research data sets that will be used for analyses, all study sites have been offered a Business Associate Agreement with the University of Utah. Copies of executed Business Associate Agreements are maintained at the DCC.

10.2 Inclusion of Women and Minorities

There will be no exclusion of patients based on gender, race, or ethnicity.

10.3 ClinicalTrials.gov Requirements

This study will not be registered at ClinicalTrials.gov as it is not an interventional trial.

10.4 Retention of Records

For federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for at least 3 years after completion of the research. Completion of the research for this protocol should be anticipated to include planned primary and secondary analyses, as well as subsequent derivative analyses. Completion of the research also entails completion of all publications relating to the research. All records shall be accessible for inspection and copying by authorized representatives of the regulatory authorities at reasonable times and in a reasonable manner [45 CFR §46.115(b)].

10.5 Public Use Data Set

After subject enrollment and follow up have been completed, the DCC will prepare a final study database for analysis. A releasable database will be produced and completely de-identified in accordance with the definitions provided in the Health insurance Portability and Accountability Act (HIPAA). Namely, all identifiers specified in HIPAA will be recoded in a manner that will make it impossible to deduce or impute the specific identity of any patient. The database will not contain any institutional identifiers.

The DCC will also prepare a data dictionary that provides a concise definition of every data element included in the database. If specific data elements have idiosyncrasies that might affect interpretation or analysis, this will be discussed in the dictionary document. In accordance with policies determined by the investigators and funding sponsors, the releasable database will be provided to users in electronic form.

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