Supplementary Online Content


Trial protocol

This supplementary material has been provided by the authors to give readers additional information about their work.
Informing Decisions in Chronic Critical Illness: An RCT

Research Protocol

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1) Objectives

We propose a randomized, controlled trial of a program of proactive, protocolized meetings in which an interdisciplinary Supportive Information Team (“SIT”) led by an attending physician with palliative care expertise provides informational support to families of chronically critically ill patients to facilitate decision-making with the ICU physician; families will also receive a printed informational aid. Our intervention will be compared to usual ICU care plus the printed informational aid. We hypothesize that the SIT intervention will inform decision-making during chronic critical illness, improve family well-being, promote discussion of patient goals of care, and optimize utilization of critical care resources, without increasing mortality. We will test this hypothesis by addressing the following Specific Aims:

Specific Aim 1: To evaluate the impact on family- and patient-focused outcomes of a proactive program of protocolized, interdisciplinary, informational support meetings led by a palliative care physician, plus a printed informational aid, for families of chronically critically ill patients.

Hypothesis 1a: This intervention will be associated with lower levels of family anxiety/depression and post-traumatic stress disorder, as compared to usual care plus the printed aid.

Hypothesis 1b: This intervention will increase discussion of preferences for patient goals of care.

Specific Aim 2: To evaluate the impact of this intervention on utilization of critical care resources for the chronically critically ill.

Hypothesis 2: This intervention will be associated with more efficient utilization of resources including shorter lengths of ICU and hospital stay and shorter duration of specific intensive care therapies, without increasing mortality.

2) Background

Advances in intensive care have enabled more patients to survive acute critical illness but created a new population who are “chronically critically ill.” Numbering more than 100,000 at any point in time, these patients fail to recover from respiratory failure and dysfunction of other organs, remaining dependent on mechanical ventilation and other intensive care therapies. Chronic critical illness is not simply a prolongation of acute critical illness but is a discrete syndrome and a devastating condition, particularly for older adults who comprise the majority of this group nationally. Distress is common both for patients
and families, hospital stays are long, resource utilization and costs are enormous. Yet return of these patients to the community is rare and 6-month mortality rates exceed those for most malignancies. Descriptive research has identified domains of information that patients, families and clinicians consider relevant and important for decision-making about continuation of treatment into the chronic phase of critical illness, but has also revealed that this information is often not clearly conveyed to patients and families. Ineffective communication has far-reaching consequences, with lasting adverse effects on decision-making, patient experience, family well-being, and utilization. In acute critical illness, evidence exists that scheduled and structured family meetings improve family- and patient-focused outcomes while optimizing use of critical care resources, without increasing mortality. Randomized controlled trials have also proven the value of printed informational aids in educating families about aspects of acute critical illness. Chronic critical illness presents special issues and challenges and no previous research has tested an intervention to inform decision-making and improve outcomes for this distinctive group of patients and their families. Research is necessary to test interventions to inform and support decision-making in chronic critical illness, which presents unique challenges, and to establish that such interventions improve family- and patient-focused outcomes.

3) Setting

This study is a multi-centered study enrolling patients from medical ICU’s at Mount Sinai Medical Center (MSMC), Durham Regional Hospital, Duke University Medical Center, and the University of North Carolina Hospitals. These sub-contracted sites will have IRB approval and will adhere to regulations and scientific and ethical guidelines.

4) Study Design

a) Recruitment Methods

The source of potential subjects will be the Medical Intensive Care Unit. The research coordinator will conduct a focused screening. Each weekday, one Research Assistant (RA-1) at each site will screen for potential subjects by asking the ICU clinical team to identify patients meeting eligibility criteria. The ICU clinicians (the primary doctor for this patient) will identify patients that are likely to be eligible for participation. Verification of eligibility through the medical record will be limited to the length of mechanical ventilation and absence of trauma, burn, and neuromuscular disease. The ICU physician will describe the study to surrogates of patients who are eligible, as well as patients with capacity to provide informed consent (we do not expect that patients will have such capacity because they will be critically ill and mechanically ventilated) and will introduce the research coordinator to the patient and family. No identifiable information will be retained. Patient capacity for consent will be evaluated by the ICU attending physician, who will consult about the patient’s capacity with the research assistant and the patient’s bedside nurse. Capacity of surrogates to provide consent will be evaluated by the ICU attending physician. We will be offering study participation to two categories of surrogates: 1) Primary Surrogate and 2) Additional Decision-Maker for the patient. The ICU attending physician will introduce the Research Assistant to potential participants, from whom the Research Assistant will seek informed research consent after a full explanation of the study.

b) Inclusion and Exclusion Criteria

Subjects will be recruited from the MICU at MSMC. The Research Assistant will screen for potential subjects by asking the ICU clinical team to identify patients meeting eligibility criteria. Chronically critically ill patients are rarely capable of communication and decision-making at this phase of illness, so the research subjects for this study include both patients meeting medical eligibility and their family or other surrogate decision-makers.
Patient inclusion criteria: Patients in the MICUs will be eligible if ≥ 21 years old, mechanically ventilated for ≥ 10 days, and chronically critically ill as defined by the ICU physician’s clinical impression that the patient will neither be liberated from the ventilator nor die in the next 72 hours. This judgment, typically triggering consideration of options including tracheotomy and continued critical care therapies, represents a practical and accepted point of demarcation between acute and chronic critical illness. Inclusion criteria for families/other surrogates: at least 21 years old; surrogate decision-maker for patient meeting patient inclusion criteria; English-speaking. We will offer study participation to two categories of surrogates: 1) Primary Surrogate and 2) Additional Decision-Maker for the patient. The Primary Surrogate is the individual who has been designated by either the patient or applicable law as having responsibility for health care decision-making if the patient lacks capacity for such decision-making. The Additional Decision-Maker refers to other family members/surrogates who expect to attend discussions related to health-care decision-making for the patient during the study and to assist the Primary Surrogate in making those decisions. We will enroll a single Primary Surrogate (together with the patient, as a dyad) and will enroll as many Additional Decision-Makers as meet the defined criteria and provide informed consent to the research.

Patient exclusion criteria: 1) Previous admission to the study ICU during the research; 2) Prior palliative care consultation during this hospitalization; 3) Chronic neuromuscular condition (e.g. ALS) requiring prolonged mechanical ventilation independent of critical illness; 4) No surrogate decision-maker; 5) Mechanically ventilated at an outside hospital for greater than 7 days before transfer; 6) Trauma; and 7) Burn. Exclusion criteria for families/other surrogates: we seek to enroll only surrogates of patients who are enrolled, and patient exclusion criteria exclude patients without surrogates who are at least 21 years old and English speaking (thus it is not necessary to specifically exclude those individuals as surrogates). In addition, patients will be excluded if there is no surrogate decision-maker, if the family is not available, or if the physician refuses permission for the research staff to approach the family.

We recognize that bias might be introduced by involvement of an investigator as the attending physician in a study ICU or as the SIT physician during this research. We will therefore temporarily suspend subject recruitment starting 5 days before and continuing through the end of the period of any investigator’s ICU services and exclude investigators as SIT physicians. All patients in this study will have critical illness and will be on mechanical ventilation and unable to communicate verbally. We expect that all or virtually all patients will also lack decision-making capacity because of sedation or medical conditions causing cognitive impairment. Thus, patient consent by an appropriate surrogate would be needed for participation by patients. The study will be enrolling surrogates and patients as dyads (surrogate/patient), along with any additional decision-makers who are eligible and provide informed consent for study participation. Given these circumstances, consent will be sought for both members of the dyad, the patient as well as the surrogate, from the surrogate, using a single participant information sheet that explains participation by each dyad member. However, if the patient has capacity to provide informed consent for the research, we will approach the patient for consent initially and, if the patient provides such consent, will approach the surrogate separately for the surrogate’s participation in the research.

Randomization

Upon completion of written informed consent, patients with family members are to be randomized to usual care or intervention study groups using the computer-generated, web-based randomization system through the DEMS at the Sheps Center in Chapel Hill. The randomization will be stratified by site in blocks varying from 8 to 10.

c) Procedures

The research will be conducted in the MICU. Patient-family dyads will be randomized at each site to receive either the full intervention (proactive family meetings plus printed informational aid) or usual ICU care plus the printed aid. The intervention meetings will be coordinated and conducted by an
interdisciplinary Supportive Information Team ("SIT") consisting of a palliative care physician and an advanced practice nurse, who will use a protocolized approach to share information and to establish a framework for goal-directed decision-making by the family with the ICU physician. Main objectives of these meetings will be to 1) determine the family’s understanding of the patient’s medical illness, prognosis, and treatments; 2) enhance the family’s understanding of chronic critical illness; 3) discuss potential burdens and benefits of continuing intensive care treatment; 4) explore relevant values of the patient and family; 5) elicit treatment preferences that the patient may have expressed; 6) align family expectations with the clinicians’ expectations of the clinical course; 7) integrate information previously received from multiple caregivers; 8) discuss expected care needs for the longer term, in light of the patient’s cognitive and functional status and level of dependence on medical and nursing interventions; and 9) contribute other information and support as needed by the family for establishing goals of care with the ICU physician. These meetings will not mandate any treatment decision but instead provide a goal-oriented context for decision-making by the family with the ICU physician. Throughout the study, the ICU physician will be involved in intervention meetings through a structured and templated process of input to and feedback from the SIT physician. In addition, the ICU physician will have the option to participate directly in SIT family meetings and, regardless of direct participation, decision-making will remain the responsibility of the ICU physician with the patient’s family.

Our study design is shown in Figure 1 below. We will measure family- and patient-focused outcomes by family interviews at study enrollment, shortly after the SIT meeting sequence (comparable time point for control subjects), and 3 months later. Primary outcomes will be Family Anxiety/Depression, Family Post-Traumatic Stress Disorder, and Discussion of Preferences for Patient Goals of Care (Specific Aim 1). To meet Specific Aim 2, we will measure utilization outcomes through prospective medical record review, while monitoring for evidence that mortality rates remain unchanged. SIT and ICU clinicians will be blinded to study outcomes and primary outcome data will be collected by Research Assistants who are blinded to group assignment. Our analyses will compare family/patient outcomes (Specific Aim 1) and utilization outcomes (Specific Aim 2) between subjects randomized to the SIT intervention or to usual care with the printed aid.

![Figure 1. Study Design](image)

Data collection will involve prospective review of medical records and direct interviews of family (or other surrogate decision-maker) subjects. Review of medical records will involve existing materials and not materials specific to this research (apart from templates to be completed by the SIT physician reflecting input from and feedback to the ICU physician. We will be collecting information on day 10, 14 and 21 for the Provent model. We will not obtain any invasive physical specimens nor perform any procedures for which informed consent is normally required outside of a research context. For patients who can respond, we will administer a cognitive screen (Confusion Assessment Method for the ICU) to evaluate for dementia or acute delirium. (Patients without delirium by this screen and without other evidence of cognitive impairment will be asked for permission to conduct intervention meetings with their family member or other surrogate decision-maker.) Apart from this screen, no data will be collected directly from patients. Patients’ medical records will be reviewed prospectively by trained research personnel for information including demographic and health characteristics (e.g., race, ethnicity, chronic co-morbid conditions, hospital and ICU admitting diagnoses, reasons for prolonged ventilator...
dependence, severity of illness, insurance status), critical care resource utilization (e.g., length of stay in the ICU, duration of mechanical ventilation), and course and outcome of illness (e.g., complications, vital status, discharge site).

Family subjects will be interviewed at 3 time points by trained Research Assistants (those who collect outcome data through these interviews will be blinded to group assignments). Two of these interviews will be conducted in-person in the hospital (Interview #1 at enrollment; Interview #2 after the SIT-2 meeting or a comparable time point for subjects in the control group); and the third interview will be conducted by telephone at 3-months after randomization (follow-up-Interview #3). These interviews will involve administration of one or more of the following instruments: Hospital Anxiety and Depression Scale, Impact of Events Scale-Revised (measuring post-traumatic stress disorder), Discussion of Preferences Subscale of the Center for Gerontology and Health Care Research Family Survey, Quality of Communication Scale, and the ICU Family Satisfaction Survey (FS-ICU 24) (measuring satisfaction with overall care, decision-making and communication). All of these instruments are brief and validated. In addition, during Interview #3, we will be asking the location of the patient or, if the patient has died, we will ask the location of death. At Interview #1 (time of enrollment), the Research Assistants will obtain demographic information about family subjects (e.g., race, ethnicity, education) and information about their relationship to the patient (spouse, adult child, sibling, etc.) The family interviews will each be completed in less than 30 minutes. If the patient dies or is discharged from the hospital before the time point for the second in-person interview, that interview will not be conducted with the family subject (since the family would not have another reason to be present at the hospital), but the family would be contacted by telephone for the 3-month follow-up interview.

RA-1 will be responsible for recruitment, administration of Interview #1, and all coordination of family meetings. RA-2 will be blinded to which group the patient is in (intervention or control) and will be administering Interview #2 and Interview #3. We will send a letter home to families to remind them of the 3-month follow-up interview. In addition, a second reminder letter, for families that are difficult to reach, will be sent home to participants after a number of failed attempts to reach the family members.

Fidelity to Protocol

We will use several methods to assure standardization of the intervention and fidelity to the protocol. The intervention to be studied in this research is designed to inform decision-making during chronic critical illness, improve family well-being, promote discussion of patient goals of care, and optimize utilization of critical care resources, without increasing mortality. The initial meeting (“SIT-1”) will take place at the onset of chronic critical illness and a second (follow-up) meeting (“SIT-2”) will take place 10 days later, which may follow a period of further intensive care treatment. (Additional SIT meetings will be conducted during the interval between SIT-1 and SIT-2 if judged to be necessary by either the SIT or the ICU physician or requested by the family.) The intervention meetings will be coordinated and conducted by an interdisciplinary Supportive Information Team (“SIT”) consisting of a palliative care physician and an advanced practice nurse, who will use a protocolized approach to share information and to establish a framework for goal-directed decision-making by the family with the ICU physician. Two meetings SIT meetings will be led by physicians with specialized training, certification, and experience in palliative care including communication skills for family meetings and the Education of Physician’s in End-of-Life Care Project (EPEC) protocol for such meetings. All SIT teams will also receive intensive and specific training on the meeting protocol from expert faculty. This training will review existing evidence about the definition, prognosis, and other relevant aspects of chronic critical illness and core skills for communicating according to the SIT protocol. The training will also emphasize the primary role of the ICU physician in patient care and decision-making. We will use role-playing and other appropriate pedagogic techniques. When the intervention is introduced, one PI and another expert faculty member
will observe two SIT-1 and two SIT-2 meetings involving each SIT team member at each site and give corrective re-training as needed.

A random sample of 24 SIT meetings (12 each, SIT-1 and SIT-2) at each study site (about 10% of the total expected number of such meetings) will be digitally audiorecorded, if consent is obtained from all meeting participants. Recordings will be transcribed and reviewed to verify coverage of topics targeted for discussion (RA-1 at Duke will have specific training and a protocol-based checklist for this purpose). Results will be fed back to SIT teams with appropriate guidance to enhance adherence and fidelity; retraining will focus on areas found deficient during monitoring. The templates for SIT meetings at each site will be audited monthly by the Project Coordinator to identify deviations from meeting protocol or inadequate documentation; these audits will continue until the site demonstrates satisfactory template completion (all items documented) for 3 consecutive months, after which audits will be performed quarterly. Training will be repeated as necessary.

d) Outcome Variables

Table 1. Family-and Patient-Focused Outcome Measures

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Measurement/Instrument</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family Anxiety / Depression</td>
<td>Score on Hospital Anxiety and Depression Scale – (HADS) – (0-42)</td>
<td>In-Person Family Interviews #1 and #2 and Telephone #3</td>
</tr>
<tr>
<td>Family Post-Traumatic Stress Disorder</td>
<td>Score on Impact of Events Scale-Revised – (IES-R1) – (0-88)</td>
<td>Telephone Interview #3</td>
</tr>
<tr>
<td>Discussion of Preferences for Patient Goals of Care</td>
<td>Discussion of Preferences for Patient Goals of Care Subscale-Ctr Gerontol Health Care Res Toolkit – (Y/N)</td>
<td>In-Person Family Interview #2 and Telephone #3</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of Physician Communication</td>
<td>Summary Score on Quality of Communication Scale – (0-9)</td>
<td>In-Person Family Interviews #1 and #2</td>
</tr>
<tr>
<td>Family Satisfaction</td>
<td>Score on Heyland Family Satisfaction in ICU – 24 Item Survey (FS-ICU-24) – (0-100)</td>
<td>(Telephone) Interview #3</td>
</tr>
<tr>
<td>Ctr Gerontol Health Care Res Toolkit</td>
<td>Full set of domains</td>
<td>(Telephone) Interview #3</td>
</tr>
</tbody>
</table>

Table 2. Utilization Outcome Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
<th>Duration*</th>
<th>Limitation (Withholding or Withdrawal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU LOS</td>
<td>Conseö days during stay that includes enrollment</td>
<td># days</td>
<td></td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>Days from admission to discharge or death</td>
<td># days</td>
<td></td>
</tr>
<tr>
<td>Tracheotomy</td>
<td>Surgical or Percutaneous</td>
<td></td>
<td>No/Yes (N/Y)</td>
</tr>
<tr>
<td>Mech Ventilation</td>
<td>Invasive, via endotracheal tube</td>
<td># days</td>
<td>N/Y; days from randomization; days ltn to death</td>
</tr>
<tr>
<td>Renal Replac’t</td>
<td>Hemodialysis or other</td>
<td># days</td>
<td>N/Y; days from randomization; days ltn to death</td>
</tr>
<tr>
<td>Vasopressor Tx</td>
<td>Medications to raise systemic arterial pressure</td>
<td># days</td>
<td>N/Y; days from randomization; days ltn to death</td>
</tr>
<tr>
<td>Artificl Nutrition</td>
<td>Tube feedings or parenteral nutrition</td>
<td># days</td>
<td>N/Y; days from randomization; days ltn to death</td>
</tr>
<tr>
<td>CPR Attempts</td>
<td>Use of ACLS Protocol</td>
<td># attempts</td>
<td>N/Y; days to entry of DNR directive</td>
</tr>
</tbody>
</table>

*Duration=Sum of days after randomization from each initiation/continuation of the therapy to each discontinuation (or discharge from the study hospital). For CPR, measure=no. of attempts with ACLS protocol, with maximum of 1 per 24-hour period after enrollment. Consec=consecutive; LOS=length of stay; Ltn=Limitation; Replac’t=replacement; Tx=treatment.

5) Analysis Plan

Overview of Analysis. The study uses a randomized, controlled design to compare the intervention (protocolized SIT meetings plus printed aid) with usual care plus the printed aid. We hypothesize that this intervention will favorably affect family-/patient-focused outcomes (Aim 1) and resource utilization outcomes (Aim 2), without increasing mortality. Family/patient-focused outcomes (Table 1, above) will be collected in two in-person interviews in the hospital and a third interview by telephone 3 months later.
Utilization outcomes (Table 2, above) will be obtained prospectively from medical records. In 5a below, we summarize descriptive analyses. We then (5b) review our primary study outcomes, Family Anxiety/Depression, Family Post-Traumatic Stress Disorder, and Discussion of Preferences for Patient Goals of Care, and summarize our basic strategy for analysis of the intervention’s effects (5c). In 5d we discuss application of this strategy to the primary outcomes. Analysis of secondary outcomes under Aim 1 and Aim 2 is discussed in 5e and 5f, respectively. We address other analytic issues in D.14.8 - D.14.10.

5a. Descriptive Analyses. We will use descriptive statistics to summarize sociodemographic characteristics of patient and family subjects and patients’ health characteristics. We expect that the randomization will achieve baseline comparability of intervention and control groups, and will confirm this result using t-tests for comparisons of normally distributed continuous variables, chi-square tests for categorical variables, and the Wilcoxon rank-sum test for non-normally distributed continuous variables. We will perform simple comparisons among sites to describe specific local characteristics of study populations, practices, or outcomes. We will also compare basic characteristics of subjects responding to all study interviews with those of subjects who do not respond to all and, to the extent possible, compare patients enrolled in the study with those for whom participation is refused.

5b. Primary Outcomes. We will compare subjects in SIT intervention and control groups with respect to: Family Anxiety/Depression (Hospital Anxiety and Depression Scale [HADS]), Family Post-Traumatic Stress Disorder (PTSD; Impact of Events-Revised [IES-R] scale), and Discussion of Preferences for Patient Goals of Care (CGHCR Toolkit-valid subscale). We selected our two measures of family well-being because they assess conditions that are known to be prevalent and distressing for ICU families and because prior research on information support strategies during acute critical illness indicates that they are responsive to appropriate intervention; both are continuous measures. Our primary patient-focused outcome, Discussion of Preferences for Patient Goals of Care, addresses the main objective of clinical discussions of disease process and prognosis in life-threatening illness – to align treatment plans with patient/family preferences, values, and goals of care. This will be a dichotomous outcome.

5c. Basic Strategy for Analysis of Intervention Effects. We will perform (generalized) multiple regression analyses in which the explanatory variables will be: (i) SIT intervention or control group assignment; (ii) multiple respondents, other selected independent variables or, where applicable, the baseline (Interview #1) level of the outcome of interest; and (iii) random center effects. For Anxiety/Depression, we will use multiple linear regression with a baseline; for PTSD, multiple linear regression without a baseline; and for Discussion of Preferences for Patient Goals of Care, multiple logistic regression without a baseline value. Random effects will be included as below.

Analysis by Intention to Treat. For analyses, each patient-family dyad will remain in the group to which originally assigned, whether or not they received the care intended for that group. Thus, intervention subjects who for any reason fail to receive the SIT meeting sequence will still be included in the intervention group, while subjects will continue in the control group even if they met with palliative care consultants.

Approach to Other Independent Variables. Family Anxiety/Depression, a primary outcome, will be measured before (at Interview #1) as well as after (at Interview #2) the intervention and at 3 months. We expect that the baseline value of this outcome will capture most of the effects of measured covariates -and those not measured. We will then evaluate the additional effects of other independent variables by performing a forward stepwise regression with the baseline value “forced in” the model. We will also use forward stepwise regression to assess effects of independent variables for the other primary outcomes -Discussion of Preferences for Patient Goals of Care, measured at Interview #2 and 3, and Family Post-Traumatic Stress Disorder, measured at Interview #3. Site, gender and race will be included in the models, as will the family or other surrogate’s relationship to the patient.
We are aware that death or time in the ICU could influence outcomes of interest. We are hesitant to include these as independent variables in the primary analysis because they are really outcomes that might themselves be influenced by our intervention. We will, however, perform secondary analyses in which these variables are predictors, and determine whether useful information is contributed by this approach.

**Approach to Random Effects.** We propose to use SAS software to analyze what we refer to as random effects, but in other contexts are referred to as Multilevel Modeling or Hierarchical Linear Modeling (For present purposes, the differences in software and terminology are, in our view, of lesser importance.) PROC MIXED can be used in multi-level models with normally distributed outcomes,\textsuperscript{145} while other PROC’s can be used for yes/no data, counts, and lengths of stay. We will specify options in the SAS programs in which the center is both a fixed effect (reflecting potentially different demographics) and a random effect. We will assume that patients within a center are all equally correlated with one another. We are aware of other approaches, including HLM, MIXXOR and MIXREG, and Bayesian methods incorporating Winbugs, which may use pairs of equations, one for center effects and one for patient effects. We do not anticipate large random center effects in our study and do not aim to evaluate center-specific explanations for the effects of our intervention. Rather, random effects methods would address the possibility of small unexplained differences in the intervention’s success according to center. We will consider using other software as needed in the course of the analyses.

**5d. Application of Methods to Primary Outcomes.** *Family Anxiety/Depression* will be measured at Interviews #1 and #2, and #3. We will focus on the data from Interview #3, since this interview will be conducted after both SIT meetings and subsequent hospital outcomes. We will use the first interview as a covariate for the outcome collected at the third interview. For this outcome, selection of independent variables is a minor issue, since the effects of any independent variables should be reflected in the baseline (Interview #1) value of the scale. Subjects without Interview #2 (e.g., those who refuse this interview, or families of patients who are discharged from the hospital or die between Interviews #1 and #2) will necessarily be excluded from analysis of the intervention’s impact on Anxiety/Depression at interview #2; the number of such subjects is expected to be small.

*Family Post-Traumatic Stress Disorder* will be measured at Interview #3 (only), conducted by telephone at three months following randomization. All families will be approached for Interview #3, even if they were unavailable for Interview #2 because the patient died or was discharged. We will select independent variables using forward selection regression.

*Discussion of Preferences for Patient Goals of Care* will be measured at Interview #2 and #3. We will not administer this measure at Interview #1 because of the possibility that this might prompt families in the control group to seek discussions of patient goals of care that might not otherwise occur.

**5e. Application of Methods to Secondary Outcomes Under Specific Aim 1 (Family-/Patient-Focused Outcomes).** *Quality of Physician Communication* will be measured on continuous scales at Interviews #1 and #2. These outcomes will be approached in the same way as the Family Anxiety/Depression outcome (5d). *Family Satisfaction* will be measured on continuous scales at Interview #3 (only), by telephone. These outcomes will be approached in the same way as the Family PTSD outcome (5d).

**5f. Application of Methods to Secondary Outcomes Under Specific Aim 2 (Utilization of Critical Care Resources).** Specific Aim 2 addresses outcomes related to critical care resource utilization, which are listed in Table 8, D.12.2. We plan to approach these outcomes using the basic strategy described previously (D.14.4). The utilization outcomes are either not continuous or, if continuous, refer to times
that may not follow a normal distribution. For such outcomes, we will use generalized mixed linear
models in which the outcome is either: (i) Yes/No (e.g., limitation of specified life-sustaining therapy; or
performance of tracheotomy), which follows a binomial distribution; (ii) Number of attempts (use of
CPR), which follows a Poisson distribution; (iii) Time to an event (e.g., number of days alive, length of
stay in the ICU or hospital); or (iv) Number of days the patient is under a certain condition regardless of
“start” or “stop” dates (this could include number of days to limitation of treatment), which may follow
either a Poisson or gamma distribution.

Outcomes of types (i) and (ii) will be analyzed by Generalized Linear Models based on a binomial or
Poisson distribution. We can also use random effects terms in these procedures to account for the random
center effects. For outcomes of type (iii), specifically for lengths of stay, we will use standard life time
methods, e.g., Kaplan-Meier, to describe time until discharge (length of stay) for SIT and control groups.
We will view death as a censoring variable. We will first evaluate the differences between the groups,
without adjusting for covariates using the logrank test, and then use Cox regression to evaluate these
differences with adjustment for covariates. The selection of covariates will be guided by the prior results
and by stepwise procedures.

Mortality, as measured by life expectancy since randomization, will be evaluated by methods similar
to those described for type (iii) outcomes. Here the censoring will generally be administrative - the end of
the observation period at three months after Interview #2; in rare cases we will also have loss to follow-
up.

For outcomes of type (iv), we will use either PROC GENMOD or GLMMIX of SAS (we prefer GLMMIX,
since GENMOD focuses on marginal models), analyzing days of intensive care therapies. As an alternative
approach to obtain a simpler overview, we will compare intervention and control groups using a chi-
square test, or a non-parametric test such as Mann-Whitney-Wilcoxon, or use normal-theory methods
following a transformation.

5g. Enrollment and Power

The enrollment period will begin October 2010 and end November 2014, corresponding to the grant
funding period. Based on previous literature, 150 family members in each group should provide a
sufficient sample to detect a minimal important difference of 1.5 units in mean HADS with 90% power
and a type-I error of 5%. Enrollment will continue until the end of the funding period to allow for drop
out and multiple respondents, and to maximize power for secondary outcomes.

6) Data Management and Confidentiality

Data obtained through abstraction of medical records and through direct interviews of family subjects
(and cognitive screening for patients who can respond, as above) will be recorded on computerized case
report forms, which will be transferred (after de-identification, as follows) to a centralized database
constructed and operated for this project by the Cecil Sheps Health Services Research Center at the
University of North Carolina (UNC). The Sheps Center will utilize a web-based system to present case
report forms and allow remote sites to key data directly into the central database. All system login
procedures and data submissions will be transported encrypted via the Secure Sockets Layer (SSL)
protocol to a secure central database at the Sheps Center. User-level permissions will be defined within
the project system to limit a user’s access to only those records an individual is authorized to see. The
central database for the project will run on a mirrored server system with automatic fail-over features,
daily backups, and transaction logs. Audit logs will be reviewed routinely to verify the security measures
are operational. The servers are currently maintained at the highest level of vendor and CERT security
recommendations. Data will never be shared outside the project unless authorized by the Principal
Investigators. User authentication is based on user passwords. Password creation requirements are in
place to guarantee “strong passwords” as defined by the CERT security recommendations. The UNC Sheps Center endeavors to preserve the privacy, confidentiality, and security of protected health information that may be part of health records or research datasets. Protected Health Information (PHI) is handled according to appropriate Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy and Security regulations. Sheps Center staff who work with PHI are required to complete appropriate HIPAA training and periodic updates. All personal computers and servers are encrypted and located in lockable offices. The server room is accessible only to designated systems administrators. Original data disks and backup disks are stored in locked offices with copies secured in at least one other off-site location.

Only a single investigator and research assistants at each site will have access to a list of identifying information for participants enrolled at that site, and this list will be unavailable as soon as data accuracy is verified and analyses are complete. At Mount Sinai, the Principal Investigator and the Project Coordinator will have this access (since the Project Coordinator will function as Research Assistant at Mount Sinai).

For a random 10% sample of subjects, we will test reliability by comparing medical record abstraction of study variables by two independent reviewers (RA-1 / Project Coordinator; records of subjects at MSMC, where the Project Coordinator will also function as RA-1, will be reviewed by that individual and RA-2). We will also examine data validity by determining sensitivity/specificity of diagnoses and co-morbid medical conditions coded by the RAs as compared with those of a physician-investigator.

Under the Administrative Supplement that has been awarded for this study, we plan to analyze transcripts of about 40 additional audio recordings from clinician-family meetings. A de-identified study ID number will be assigned to each audio file and only the Project Manager at Mount Sinai Medical Center will have access to the study subject names corresponding to these numbers. The transcriber will be given limited access to the Sheps datacenter site (please see information regarding security of Sheps datacenter site above) to ensure the secure exchange of the (numerically-identified) audio files for transcription. This access will permit the transcriber only to access the audio files for transcription and to return the completed transcripts (and the audio files from which they were transcribed). In the transcripts, participants will be referred to with de-identified, generic terms - e.g., Clinician 1, Family Member 1 (Male), Family Member 2 (Female). The Project Manager will retrieve the transcripts (and, after transcription, will remove the audio files) from the secure site. Finally, the de-identified transcripts will be analyzed and coded by members of the investigative team using ATLAS.ti qualitative analysis software. When the analyses and reports are complete, the audio files, transcripts, and list of study participants’ names corresponding to the numeric study IDs will be destroyed.

**Protocol Modifications**

September 2011: Patients will be eligible for enrollment if they require at least 7 days of mechanical ventilation; changed from 10 days.