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"Protocol for a Randomized Trial of an Interprofessional Team-delivered Intervention to Support Surrogate Decision Makers in ICUs."

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PARTNER Intervention Protocol

ABSTRACT

Introduction: Although shortcomings in clinician-family communication and decision-making for incapacitated, critically ill patients are common, there are few rigorously tested interventions to improve outcomes. In this manuscript, we present our methodology for the **Pa**iring **R**e-engineered ICU **T**eam with **N**urse-driven **E**motional support and **R**elationship-building (PARTNER 2) trial, and discuss design challenges and their resolution.

Methods and Analysis: This is a pragmatic, stepped-wedge, cluster randomized controlled trial comparing the PARTNER 2 intervention to usual care among 690 incapacitated, critically ill patients and their surrogates in 5 ICUs in Pennsylvania. Eligible subjects include patients at high risk of death and/or severe long-term functional impairment, their main surrogate decision-maker, and their clinicians. The PARTNER intervention is delivered by the interprofessional ICU team and overseen by 4-6 PARTNER nurses per ICU. It involves: 1) advanced communication skills training for nurses from each ICU to deliver support to surrogates throughout the ICU stay; 2) deploying a structured family support pathway delivered by the interprofessional ICU team; 3) enacting strategies to foster collaboration between ICU and palliative care services; and 4) providing intensive implementation support to each ICU to incorporate the family support pathway into clinicians' workflow. The primary outcome is surrogates' ratings of the Quality of Communication during the ICU stay as assessed by telephone at 6 month follow up. Prespecified secondary outcomes include surrogates' scores on the Hospital Anxiety and Depression Scale, the Impact of Event Scale, the modified Patient Perception of Patient Centeredness (PPPC) scale, the Decision Regret Scale, nurses' scores on the Maslach Burnout Inventory, and length of stay during and costs of the index hospitalization.

Here, we discuss key methodological challenges including determining the optimal level of randomization, using existing staff to deploy the intervention, and maximizing long-term follow-up of participants

Summary of Methodologic Strengths and Limitations:

- Use of existing staff to deploy the intervention
- Need for in-person training of staff will necessitate creative solution for broad dissemination
- Multifaceted approach to maximizing long-term follow-up of participants
- Challenge of selecting a single primary endpoint for a multicomponent ICU-level intervention

Keywords: statistics and research methods, adult intensive & critical care, clinical trials, adult palliative care

PARTNER Intervention Protocol

INTRODUCTION

Approximately one in five Americans die in or shortly after discharge from an intensive care unit (ICU.)[1] Many of these deaths occur following a decision to withhold or withdraw life-prolonging therapies.[2-13] Because critically-ill patients often lack decision-making capacity, surrogate decision-makers are asked to assist in making these difficult decisions. A large body of research has documented problems with the process and outcomes of surrogate decision-making in ICUs, including frequent failure to discuss patients' values, provide emotional support, hold timely family meetings, or explain treatment options such as comfort-focused care.[14-18] Surrogates in ICUs perceive their role as challenging[19-21] and experience high levels of depression, anxiety, and PTSD.[22,23] There is also evidence that critically-ill patients often receive more intensive life-extending treatment than they would choose for themselves, which is problematic because of the impact on both individual patients and the costs of medical care near the end of life.[24,25]

Although the scope of problems with surrogate decision-making for critically-ill patients is well-documented, there are few evidence-based strategies to improve patient, family, and health system outcomes in patients with advanced critical illness.

We therefore developed a multi-component intervention delivered by the interprofessional ICU team to provide structured support of families throughout the ICU stay.[26-28] The intervention is designed to follow to national recommendations to utilize interdisciplinary teams to support patients and families[29,30] and leverage nurses' professional orientation toward providing patient and family-centered care.[31,26-28] Herein we present the trial methodology describe the study intervention, and discuss our approach to three key methodological challenges – determining level of randomization, integrating the intervention with existing clinical staff, and achieving long-term follow-up.

METHODS

Overview of Trial Methodology

This is a pragmatic, stepped-wedge, cluster randomized controlled trial evaluating the PARTNER intervention compared to usual care control. We will assess the effect on three domains of outcomes: measures of the patient-centeredness of care and quality of clinician-family communication, surrogates' symptoms of long-term psychological distress, and healthcare utilization.

Trial Centers and Participants

The trial is being conducted in five ICUs at four hospitals in Pennsylvania within the UPMC Health System: three medical ICUs within three community hospitals in which intensivist physicians served as the attending physician of record for all patients, and a cardiac ICU and cardiothoracic surgical ICU within one academic hospital, in which in which intensivist physicians provided care for all patients in collaboration with a primary attending physician.

The trial includes all patients in the study ICUs who meet eligibility criteria during the enrollment period. Detailed inclusion and exclusion criteria are summarized in Table 1 for patients, surrogate decision-makers and nurses. Inclusion criteria for patients includes an age of 21 years or greater, lack of decision making capacity, and at least one of the following: receipt of mechanical ventilation for at least four consecutive days, judgment by the attending physician that the patient has at least a 40% chance of death during the hospitalization or at least a 40% chance of severe long-term functional impairment. Research staff enrolled one surrogate decision maker per patient whom the family identified as the patient's main surrogate. Nurses were eligible if they were full time staff nurses in the ICU during the study period.

The study will be overseen by an independent Data and Safety Monitoring Committee (DSMC) consisting of three members with collective expertise in biostatistics, health services research, critical care medicine, behavioral interventions, and bioethics. No interim analyses will be conducted. The DSMC will monitor patient accrual, retention, and adverse events using a prespecified adverse event reporting protocol. The DSMC is empowered to stop the trial if evidence emerges of unexpectedly high rates of adverse events related to the intervention. Protocol amendments were made in consultation with the trial's DSMC and the funding agency.

Patient and Public Involvement

Patients and the public were not directly involved in the design, recruitment, or conduct of this study. However, research questions and outcomes measures were developed and informed by patient and surrogate priorities, experiences, and preferences.[14-25]

Description of the PARTNER Intervention

The PARTNER intervention is conceptually grounded in the Cognitive Emotional Decision Making (CEDM) framework and Ottawa Decision Support Framework (ODSF).[33,34] The CEDM framework views medical decisions as influenced by not only cognitive and informational considerations, but also the emotional

distress that arises from witnessing a critically ill loved one and being required to make difficult, highly consequential decisions for them. The ODSF conceives that better patient/family decision-making can be achieved by 1) identifying decision support needs; 2) providing tailored decision support and 3) evaluating the decision-making process and outcomes.[33,35]

The PARTNER intervention is deployed at the level of individual ICUs and is delivered by the interprofessional ICU team. It is overseen by four to six nurses in each ICU called the PARTNER nurses, who were nominated by their ICU director because they were judged to possess strong communication skills. The intervention entails guideline-recommended strategies for providing emotional support to surrogates and for ensuring frequent clinician–family communication.[31,36,37] The four main components, detailed below, are: 1) advanced communication skills training for 4-6 nurses from each ICU to deliver support to surrogates throughout the ICU stay; 2) deploying a structured family support pathway delivered by the interprofessional ICU team 3) enacting strategies to increase the timely consultation of palliative care clinicians when appropriate; and 4) providing comprehensive implementation support to ensure reliable delivery of the PARTNER intervention (Table 2.)

Advanced communication Skills Training for PARTNER nurses: PARTNER nurses from each ICU participate as a group in a 12-hour standardized, skills-focused training to develop the skills needed to support the surrogates of patients with advanced critical illness, summarized in Table 2. The training program for the PARTNER nurses adheres to best practice recommendations from the NIH Behavior Change Consortium.[38] The teaching methods are grounded in principles of self-efficacy and adult learning theory[39] and include: didactic explanation of the skill; demonstration by an expert clinician; small group practice with experiences medical actors portraying families; and structured learner-centered feedback provided by an expert educator.

Deploying a structured family support pathway delivered by the interprofessional ICU team
After the nurses are trained in communication skills for the PARTNER intervention, each ICU institutes the family support pathway. The pathway involves the PARTNER nurses meeting with families daily, according to a standardized protocol, and arranging interdisciplinary clinician–family meetings (IDFM) within 48 hours after enrollment and every 5 to 7 days thereafter. In addition, the PARTNER nurses meet with families before and after each IDFM to prepare them for the meeting and to debrief after the meeting. They also huddle with the clinical team before each family meeting. The main objectives of each encounter are summarized in Table 2 and depicted in timeline format in Figure 1.

The PARTNER intervention uses strategies from behavioral economics and implementation science to overcome barriers to achieving frequent, structured IDFMs. For example, the intervention resets the care default regarding timing of IDFMs by switching from an “opt-in” to an “opt-out” approach to scheduling. Specifically, the PARTNER nurses will schedule family meetings per protocol unless the attending physician takes active steps to override the protocol, rather than requiring the clinical team to take active steps to schedule IDFMs.

Deploying strategies to increase collaboration between Palliative Care and ICU services: We will use three strategies: 1) recruiting a PC physician champion in each ICU to spearhead increased involvement of PC services; 2) facilitating a process in each ICU in which clinicians develop a set of suggested “triggers” for PC consultation;[40,41] and 3) conducting twice weekly, in-person meetings between ICU and PC champions to assess whether any patients receiving the PARTNER intervention may benefit from a PC consultation.

Providing Comprehensive Implementation Support: The strategy for deployment is grounded in best practice recommendations to change clinician behavior and enact system-level interventions.[42] Our approach to implementation is informed by the theory of planned behavior, which holds that success is determined by the strength of providers' motivation to engage and their perceived degree of control to implement the intervention, which is largely influenced by perceived self-efficacy and organizational factors.[43,44]

We use five main techniques to encourage adherence throughout the study:

Engagement of hospital and ICU leadership: Prior to deployment at each site, study investigators meet with hospital and ICU leadership to secure their endorsement of the PARTNER intervention. These leaders sent emails hospital-wide endorsing the intervention, as well as tailored emails to all ICU clinicians encouraging them to actively participate.

Recruitment of PARTNER champions: We identified local nursing, critical care, and PC champions in each ICU. These individuals commit to taking a leadership role for promoting the intervention and assisting with implementation challenges.

Orientation of all staff to PARTNER intervention: We provided ICU physicians and bedside nurses with a structured orientation to the new care model and PARTNER nurses' role responsibilities.

On-site implementation support: During the first two weeks of deployment, an implementation specialist is on-site to provide daily assistance. Thereafter, the implementation specialist makes weekly visits to directly observe the clinicians deploying the intervention, provide feedback, and assist in overcoming implementation challenges.

Quarterly audit and feedback: The study team provides each ICU with feedback on the extent to which the intervention is being deployed as planned with statistics summarizing the number of patients enrolled, proportion who received IDFMs per protocol, frequency and timing of IDFMs compared to control phase, and frequency and timing of PC consults compared to control phase.

Description of Usual Care Arm:

The control treatment consists of usual care. No study ICU has a protocolized approach to family communication or required family meetings to be conducted at set times. At the time of the study, none of the ICUs receive implementation support, audit, or feedback related to family support and communication. Palliative care consultation is available in all study ICUs.

Randomization

The unit of randomization is the individual ICU. Study statistician' used a computer generated randomization scheme to determine the order in which ICUs transition from the control phase to the intervention phase (Table 3). All ICUs receive the intervention by the end of the study period.

Blinding

The study staff who performed chart abstraction and telephone follow-up of participants to ascertain study outcomes were blinded to participants' treatment-group assignment. The nature of the intervention made it infeasible to mask physicians and surrogates to the patients' treatment-group assignment.

Outcomes

We developed an outcome assessment strategy to measure the effect of the intervention on three interrelated issues: the quality of communication and patient- and-family centeredness of care processes, surrogates' long-term psychological distress, and healthcare utilization and costs (Table 4.)

The primary outcome measure is surrogates' total score on the Quality of Communication (QOC) scale, measured during telephone follow-up 6-months after patient's discharge from the index hospitalization. The Quality of Communication (QOC) Scale is a 13-item scale measuring quality of communication with good internal consistency, strong evidence of reliability and validity,[45,46] and established responsiveness to change.[47] The QOC scale is a patient and family-centered outcome because it measures aspects of care rated as highly important to families. Higher scores on the QOC scale have been associated with higher ratings of the patient centeredness of care[48], more goal concordant care, and shorter duration of ICU care before death.[48,49]

The investigative team originally planned to use as the primary outcome surrogates' scores on the Hospital Anxiety and Depression Scale (HADS) at 6 months follow up. However, this plan was revised based on accumulating evidence that the type of intervention tested in this trial (i.e., an intervention restricted to the ICU setting and delivered by the interprofessional ICU team) is unlikely to modify surrogates' long-term symptoms of anxiety and depression.[50-52] The change in primary outcome measure was made in consultation with the trial's DSMC and the funding agency. The decision was based entirely on new evidence external to the trial. At no time did investigators have access to outcome data from the trial, which will not be made available to investigators until the trial is complete.

Secondary outcome measures include the following measures, assessed by surrogates at 6-month telephone follow up:

Measures of Communication and Decision Quality:

Patient- and family-centeredness of care: measured with the Patient Perception of Patient Centeredness (PPPC) scale, modified for use by surrogates. The PPPC is a 12-item instrument that has established validity and reliability.[53,54]

Decisional regret: measured with the Decisional Regret Scale (DRS), a 5-item assessment of "distress or remorse after healthcare decisions." It has high internal consistency and convergent validity.[55]

Surrogates' Psychological Distress:

Anxiety and depressive symptoms: The Hospital Anxiety and Depression Scale (HADS) is a 14-item, two-domain instrument used to study anxiety and depression with established reliability and validity among ICU surrogates.[27,56-61]

Symptoms of post-traumatic stress disorder: The Impact of Events Scale (IES) is a 15-item tool measuring total stress with subscales for intrusiveness and avoidance.[62] It has been successfully used among ICU surrogates.[22,27]

Patients' Outcomes:

Discharge disposition: We will use UPMC administrative records to determine if patients were discharged to home, hospice, a skilled nursing facility, another acute care hospital, and a long-term acute care facility.

Mortality: We will assess mortality during the index hospitalization and through 6-month follow-up using hospital records, telephone interviews with surrogates at 6-month follow-up, and the Social Security Death Master File in cases if participants are lost to telephone follow-up.

Functional status at 6 months: We will assess patients' functional status at 6-months after discharge using the Katz ADL instrument completed by surrogates during the 6-month follow-up call.[63]

Healthcare Utilization and Costs:

ICU and hospital length of stay: We will determine the intervention's impact on patients' ICU and hospital length of stay, measured from study enrollment using the UPMC electronic medical record.

Total hospitalization costs: We will measure costs during the index hospitalization using the UPMC computerized cost accounting system, which assigns specific costs to each service based on hospital expenses. UPMC developed this activity-based costing (ABC) system to align costs with patients based on actual utilization of resources. Direct expenses, such as blood products, drugs, and supplies, are allocated on a patient-incurred basis. Departmental labor and other expenses are allocated to patients using specific cost drivers, such minutes on a nursing unit or time in an OR. This costing method excludes expenses related to physician margin (Physician Services Division Sweep and Support), Enterprise Shared Services, and other fully indirect expenses. These excluded categories total approximately 25% of total hospital expenses. Because this costing system excludes these fixed costs, the costs may alternatively be labelled "total controllable hospitalization costs". Further details of the activity-based costing system can be found at: https://www.healthcatalyst.com/success_stories/activitybased-costing-in-healthcare-service-lines-upmc. To calculate direct variable costs, we will remove the fixed costs of overhead that are not related to patient throughput, determined through individual departmental usage patterns and will aggregate each patient's total service specific costs.[64]

Healthcare utilization through 6-month follow up: We will measure healthcare utilization that occurs between index hospitalization discharge and 6-month follow up using an established method based on in-depth interview with the patient's surrogate during the 6-month follow-up call.[65] The interview contains questions to determine the number of post-discharge hospital admissions, nursing home admissions, emergency department visits, physician visits, hospice use, and home health service utilization.

Cost of Implementing PARTNER Intervention: To calculate costs to implement the intervention, we will determine the cost of all training, inclusive of salary/fringe costs of nurses, actors, and instructors. We will also include costs related to ongoing implementation support during the intervention phase of the study, including the implementation specialists' time, mileage and parking for travel between sites.

Statistical Methods

All analyses will be performed on an intention-to-treat basis. The individual ICU is the unit of randomization and individual surrogate/patient is the unit of analysis. To compare surrogates' characteristics across treatment groups, we will use t-tests or Wilcoxon rank-sum tests for continuous outcomes and chi-square or Fisher's exact tests for categorical outcomes. To determine whether the intervention impacts QOC scores (as well as other continuous secondary outcomes), we will use generalized linear mixed model (GLMM)to account for temporal and clustering effects typically encountered in stepped wedge clinical trial designs.[66,67] Clustering effects by ICU will be treated as random in the models. We will include time as fixed effects to account for secular trends over time and include time by treatment interaction to investigate whether treatment effect is time-varying. The model will also include random slopes of time to account for possible heterogeneous temporal effects across ICUs.

We will adjust analyses for patient age, modified SAPS III, Elixhauser index, mechanical ventilation usage, and admission source. In addition, if there are baseline differences between other demographic characteristics across treatment arms, we will adjust for those associated with the outcome in univariate analysis with a p-value less than or equal to 0.20. Should missing data prove problematic we will use the methods of multiple imputations or inverse probability weighting.[68] Final models will be assessed for stability using routine model diagnostics to identify potential outliers and/or influential observations.

Sample Size Determination. With a sample size of 690 surrogates, assuming 20% loss to follow-up and alpha=0.05, we have 80% power to detect a small effect size difference (Cohen's d: 0.30) between groups on the QOC scale. The MCID for the QOC scale has not been established, but differences between groups of this magnitude were observed in a recent trial of a family support intervention in ICUs and were associated with improved ratings of patient- and family centeredness of care (measured with the modified Patient Perceptions of Patient-Centeredness scale), as well as a shortened ICU and hospital length of stay among dying patients.[48] In addition, a recent trial of an intervention to improve communication about goals of care yielded significant improvements in the QOC with a Cohen's d of 0.56, which were in turn associated with improved rating of goal-concordant care among patients with stable goals through 3-month follow-up.[49]

The power calculation was done via NCSS PASS 15 using the pooled outcome standard deviation (SD=24.5) and coefficient of variation (COV=0.15) from the Family-Support Intervention in Intensive Care Units study.[48] We assumed a two-sided alpha level of 0.05 and a conservative estimate of 20% for the rate of surrogate loss to follow-up.

Ethics and Dissemination

Research Ethics Approval: The institutional review board of the University of Pittsburgh and the quality improvement committee of the UPMC Health System approved the project. The leadership of each participating ICU also approved the project. The intervention was judged to be a quality improvement initiative. Surrogates of eligible patients were informed of the QI project by ICU staff. The long-term follow-up of surrogates and nurses was judged to be research. Surrogate consent was obtained over the phone by research coordinators and nurses were provided written informed consent for their participation. The trial was registered on ClinicalTrials.gov before enrollment commenced (NCT02445937).

DISCUSSION

While planning the trial, we identified three key design and implementation challenges: 1) determining the optimal type of randomized trial design, 2) using existing clinical staff to deploy the intervention, and 3) maximizing long-term follow-up.

We chose to use a stepped wedge cluster randomized design rather than an individual-level RCT or a cluster RCT for two main reasons. First, we judged that randomizing individual patients within ICUs would create a high risk of contamination of the control arm because the intervention is deployed at the ICU-level. Second, a cluster RCT would involve randomly assigning half of the ICUs to receive the intervention and half to receive the control for the duration of the study. Individual ICUs were unwilling to be randomized to a control condition for the duration of the study because of mounting societal pressure to improve end-of-life care for patients with advanced critical illness. We ultimately selected a stepped-wedge cluster randomized design allows randomization at the ICU-level and allows all ICUs to receive the intervention during the study period.

We elected to use existing clinical staff to deploy the intervention for two main reasons. First, doing so increases the scalability of the intervention compared to either using research personnel to deliver the intervention to adding additional clinical personnel to the ICU care team to deliver the intervention. Second, we hypothesize that achieving durable improvements in family support will require changing ICUs' overall culture and processes of care, which may be more likely to occur when the intervention targets the entire interprofessional team rather than external interventionists.

Deploying the PARTNER intervention through the existing interprofessional team also presents several challenges. First, ICU clinicians are busy and the PARTNER intervention will likely result in an increase in the amount of time devoted to clinician-family communication. We address this by providing on-site support to develop efficient care processes and training multiple PARTNER nurses per unit. Second, few frontline clinicians have experience deploying complex, protocolized behavioral interventions, which may pose threats to intervention fidelity. We addressed the potential issue by developing a rigorous training program that focuses on the need for high adherence to protocol. In addition, we designed an extensive monitoring programming that involves weekly site visits with direct observation and coaching by implementation specialists, quarterly "booster" training sessions in which key communication skills are reviewed, and quarterly audit and feedback sessions where unit adherence is summarized.

The third challenge is achieving adequately high rates of long-term follow-up. Long-term follow-up can be challenging in this population because most of the participants will either be recently bereaved or will be caregivers for survivors of critical illness. We developed three strategies to maximize retention during the follow-up period. First, we collect extensive contact information at initial consenting including phone numbers, mailing addresses, and email addresses of both the patient's surrogate and an alternate contact who will know how to contact the participant if the surrogate's contact information is no longer valid. Second, we seek to maintain contact with the surrogate after hospital discharge beginning with a thank you note following the consenting process. We also send participants a letter 4-month post-hospitalization with information on scheduling the 6-month follow-up call at their convenience. Third, we developed a protocol for subjects who were hard-to-reach outlining appropriate use of retention strategies, such as voicemail, a hard-to-reach letter, mail return service requesting, use of the alternate contact, online searches for new information, and a version of the follow-up interview to complete via mail. We ensure these protocols are implemented through use of software with detailed record of all follow-up activities.

Conclusions

We aim to assess the impact of a theoretically-grounded intervention delivered by the existing interprofessional ICU team on the quality and patient-centeredness of communication, surrogates' psychological outcomes, and healthcare costs. Our approach to trial design and implementation may be of use to others testing complex behavioral interventions in ICUs.

Table 1. Eligibility criteria

Patient	
Inclusion criteria	Age ≥21 years Lack of decision making capacity as determined by the clinical examination of the attending physician At least one of the following: 1. ≥96hrs of mechanical ventilation 2. ≥40% chance of hospital mortality as judged by the patient's attending physician 3. ≥40% chance of severe long-term functional impairment as judged by the patient's attending physician
Exclusion criteria	Lack of surrogate decisions maker Imminent organ transplantation
Surrogate	
Inclusion criteria	Clinical surrogate decision-maker, identified as the person making decisions for the patient
Exclusion criteria	Age <18 years Unable to read and understand English Unable to cannot complete questionnaires due to physical or cognitive limitations
Clinician	
Inclusion criteria	PARTNER nurses (e.g. nurse leaders, social workers) Treating clinicians (e.g. bedside nurses)
Exclusion criteria	None

Table 2. Four Components of the PARTNER Intervention

1. Advanced Communication Skills Training for 4-6 Nurses From Each ICU to Deliver Support to Surrogates Throughout the ICU Stay	
Duration	12 hours
Teaching Methods	Didactic explanation of skills to be learned Demonstration of the skill by an expert clinician Small group practice with simulated families • Learners receive feedback from and observe each other interact with simulated families • Structured-learner centered feedback provided by an expert communication skills educator
Core Skills	Interacting with families: • Establishing emotional supportive relationships • Daily check-ins with the families to elicit questions or concerns and provide update on the plans for the day. • Preparing families for IDFM by explaining meeting goals, eliciting the patient's values, and helping them formulate their main question using a question prompt[103,104] • Attending family meetings to emotionally support the family and, if needed, use prompting skills to ensure that the families' main questions are addressed. Interacting with providers: • Conveying family questions and concerns to providers before IDFMS • Verbal prompting and persuasion to ensure structured, regular clinician-family communication • Ensuring care coordination when new clinicians come on service Documenting family meetings
Ongoing training	Quarterly "booster" training sessions in which key skills are reviewed and practiced
2. Deploying a Structured Family Support Pathway Delivered by Interprofessional ICU Team	
First Meeting with Family	Performs introduction Provides emotional support using NURSE behaviors Gets to know the family and the patient as individuals Orients the family to the ICU
Before Interdisciplinary Meeting with Family	Provides emotional support Explains what to expect in the meeting Elicits main concerns and completes question prompt list
Interdisciplinary Meeting with Family	Provides emotional support Ensures that the family's main questions are answered Brings the conversation back to the patient as an individual

	Ensures that the treatment options are discussed Ensures that there is a clear follow-up plan
After Interdisciplinary Meeting with the Family	Attends to emotions raised during the meeting Elicits questions Corrects any misunderstandings of issues addressed during the meeting
Daily Check-In	Check in daily to see how the family is doing Updates the family on the plan for the day Provides emotional support Elicits questions and concerns

3. Enacting Strategies to Increase Collaboration between ICU and Palliative Care Services

	Establishing a "Palliative Care Champion" Provision of recommended "triggers"† for PC consultation Twice weekly, in-person meetings between PC and ICU services to review the ICU census

4. Providing Comprehensive Implementation Support to Deploy the Intervention in Each ICU

Engagement of Hospital and ICU Leadership	Prior to implementation, study investigators sought explicit endorsement of the PARTNER program from hospital and ICU leadership at each site.
Recruitment of PARTNER Physician and Nurse Champions	We will identify local nurse and critical care physician leaders at each site to act as a champion. These individuals commit to taking a leadership role for promoting the intervention and assisting with implementation challenges.
Orientation of All Staff to the Intervention	Study investigators will provide ICU physicians and bedside nurses with a structured orientation to the new care model and PARTNER nurses' role responsibilities via email communications and in-person education sessions.
On-site Implementation Support	During the first two weeks of deployment, an implementation specialist is on-site to provide daily assistance. Thereafter, the implementation specialist makes weekly visits to directly observe the clinicians deploying the intervention, provide feedback, and assist in overcoming implementation challenges.
Quarterly Audit and Feedback	Audit-generated feedback on site performance of key process measures: number of patients enrolled, proportion who received IDFMs per protocol, frequency and timing of IDFMs compared to control phase, and frequency and timing of PC consults compared to control phase

[PARNTER - Pairing Re-engineered ICU Team with Nurse-driven Emotional Support and Relationship-building, ICU – intensive care unit.]

*Evidence-based strategies include the skills summarized in the NURSE mnemonic[69]

†Proposed by expert working group, as summarized by Weissman and Meier[40] and a suggested consensus-building strategy from the IPAL-ICU working group.[41]

Table 3. Randomization results and the order of sites shifting to intervention phase with target timeline and accrual.

Site	2015				2016				2017				2018			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
	CONTROL				INTERVENTION											
Community Hospital 1 MICU	Target=23				Target=115											
Community Hospital 2 MICU	Target=46							Target=92								
Academic Hospital CTICU	Target=69								Target=69							
Community Hospital 3 MICU	Target=92										Target=46					
Academic Hospital CCU	Target=115												Target= 23			

Table 4. Outcomes

Domain	Outcomes	Instrument Used	Data Source	Timing of measurement
Surrogate Decision Maker Outcome				
Measures of Communication and Decision Quality	Quality of communication	Quality of Communication Scale (QOC) [§]	Survey	6-month follow-up from enrollment
	Patient-centeredness of care	Patient Perception of Patient Centeredness (PPPC)[‡] scale, modified for use by surrogates. The	Survey	6-month follow-up from enrollment
	Decisional regret	Decisional Regret Scale (DRS)	Survey	6-month follow-up from enrollment
Psychological Symptoms Burden	Anxiety and depression	Hospital Anxiety and Depression Score (HADS) *	Survey	6-month follow-up from enrollment
	Post-traumatic stress	Impact of Events Scale (IES) [†]	Survey	6-month follow-up from enrollment
Healthcare Costs				

Payer Perspective	Index hospitalization cost		Hospital billing records	Post-discharge
	Post-discharge health care utilization		Hospital billing records, medical records and surrogate interview	6-month follow-up from enrollment
	Hospital readmission rates		Surrogate	6-month follow-up from enrollment
Hospital Perspective	Index hospitalization costs		UPMC health systems' Computerized cost accounting system	Post-discharge
	ICU and hospital length of stay		Registration data, chart abstraction	Post-discharge
	Intervention costs		Administrative records of cost of training and follow-up (salary costs, training, costs, and costs to supervise and deploy the intervention)	Post-discharge
Patient-Centered Outcomes				
	Discharge disposition (including in hospital mortality)		Registration data, chart abstraction	Post-discharge
	Functional status at 6 months	Katz ADL[¶]	Surrogate	6-month follow-up from enrollment
	Living situation at 6 months		6-month follow-up with surrogates	6-month follow-up from enrollment
	All-cause 6-month mortality		Hospital records, 6-month follow-up with surrogates, and the National Death Index	6-month follow-up from enrollment

Clinician Outcomes				
	Clinician burnout	Maslach Burnout Inventory**	Bedside nurses caring for patients enrolled in the study	Baseline, 6-month after randomization
Process Measures				
	Frequency of multidisciplinary communication		Chart abstraction	Post-discharge
	Palliative care and ethics consultations		Chart abstraction	Post-discharge
	Social work involvement		Chart abstraction	Post-discharge
	Pastoral care involvement		Chart abstraction	Post-discharge
	Incidence and timing of life support decisions		Chart abstraction	Post-discharge

*HADS is a 14-item assessment with subscales for anxiety and depression. Each domain has a score range of 0-21 with the following interpretation: 0-7 normal, 8-10 borderline abnormal, and 11-21, abnormal.

†IES is a 15-item tool measuring total stress (score range of 0-75) with subscales for intrusiveness (score range 0-35) and avoidance (score range 0-40). Total stress score is interpreted as follows: 0-8 subclinical range, 9-25 mild range, 26-43 moderate range, and 44 severe range. A score of ≥30 indicates a high risk of post-traumatic stress disorder (PTSD). The IES is a valid, reliable, and responsive 15-item instrument measuring symptoms of avoidance and intrusive thoughts.[62] It has been successfully used among ICU surrogates.[22,27]

‡PPPC is a 12-item instrument that measures the patient-centeredness of care and has demonstrated validity and reliability when used by surrogates. (Cronbach's α = 0.71)[53] A recent systematic review found the PPPC to be one of two best instruments to measur this construct.[54]

§QOC is a 13-item scale measuring quality of communication with good internal consistency (alpha = 0.94), strong evidence of reliability and validity[45,46] and established responsiveness to change.[47] The total score ranges from 0-100, with neither floor (0) nor ceiling (100) effects.

DRS is a 5-item assessment of "distress or remorse after healthcare decisions." It has high internal consistency and convergent validity.[70]

¶ Katz ADL

** Maslach Burnout Inventory is a validated, widely used measure of clinician burnout.[71-73]

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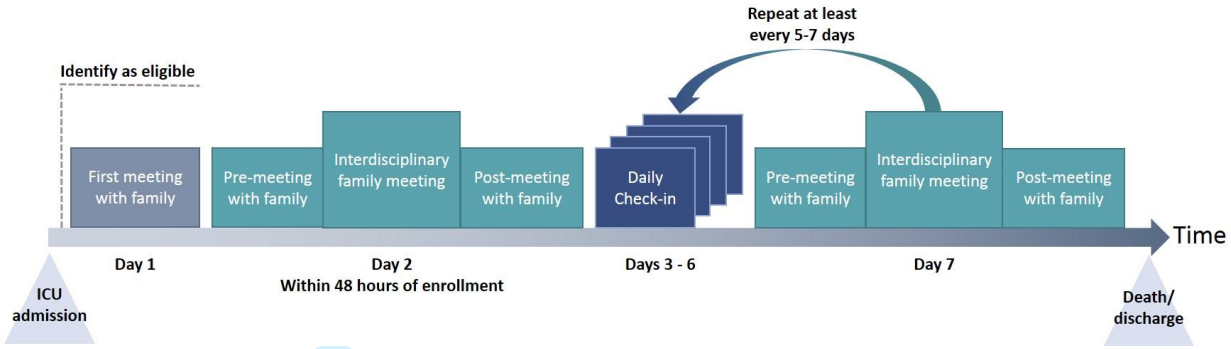
Competing interests statement: None

Figure 1. Family Interaction with the PARTNER Nurse in the Family-Support Pathway



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4, Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4-6, Table 2, Fig.1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5-6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8, Table 4
Participant timeline	13	Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig. 1, Table 3

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	6,8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-8, Table 4
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	4
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	4
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	4
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	4
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	4

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
	31b	Authorship eligibility guidelines and any intended use of professional writers	22
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Protocol for a Randomized Trial of an Interprofessional Team-delivered Intervention to Support Surrogate Decision Makers in ICUs

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"Protocol for a Randomized Trial of an Interprofessional Team-delivered Intervention to Support Surrogate Decision Makers in ICUs."

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ABSTRACT

Introduction: Although shortcomings in clinician-family communication and decision-making for incapacitated, critically ill patients are common, there are few rigorously tested interventions to improve outcomes. In this manuscript, we present our methodology for the **Pa**iring **R**e-engineered ICU **T**eam with **N**urse-driven **E**motional support and **R**elationship-building (PARTNER 2) trial, and discuss design challenges and their resolution.

Methods and Analysis: This is a pragmatic, stepped-wedge, cluster randomized controlled trial comparing the PARTNER 2 intervention to usual care among 690 incapacitated, critically ill patients and their surrogates in 5 ICUs in Pennsylvania. Eligible subjects will include critically ill patients at high risk of death and/or severe long-term functional impairment, their main surrogate decision-maker, and their clinicians. The PARTNER intervention is delivered by the interprofessional ICU team and overseen by 4-6 nurses from each ICU. It involves: 1) advanced communication skills training for nurses to deliver support to surrogates throughout the ICU stay; 2) deploying a structured family support pathway; 3) enacting strategies to foster collaboration between ICU and palliative care services; and 4) providing intensive implementation support to each ICU to incorporate the family support pathway into clinicians' workflow. The primary outcome is surrogates' ratings of the Quality of Communication during the ICU stay as assessed by telephone at 6-month follow up. Prespecified secondary outcomes include surrogates' scores on the Hospital Anxiety and Depression Scale, the Impact of Event Scale, the modified Patient Perception of Patient Centeredness scale, the Decision Regret Scale, nurses' scores on the Maslach Burnout Inventory, and length of stay during and costs of the index hospitalization.

We also discuss key methodological challenges, including determining the optimal level of randomization, using existing staff to deploy the intervention, and maximizing long-term follow-up of participants

Ethics and Dissemination: We obtained ethics approval through the University of Pittsburgh, Human Research Protection Office. The findings will be published in peer-reviewed journals.

Summary of Methodologic Strengths and Limitations:

- Strength: Use of existing clinical team in the study ICUs to deploy the intervention
- Strength: Multifaceted approach to maximize retention of participants for long-term outcome assessment
- Limitation: Need for in-person training of clinicians will necessitate a creative solution to allow broad dissemination
- Limitation: Absence of a "gold standard" primary endpoint for interventions related to communication and decision making in ICUs

Keywords: statistics and research methods, adult intensive & critical care, clinical trials, adult palliative care, nursing, communication

PARTNER Intervention Protocol

INTRODUCTION

Approximately one in five American deaths occur in or shortly after discharge from an intensive care unit (ICU).[1] Many of these deaths occur following a decision to withhold or withdraw life-prolonging therapies.[2-13] Because critically-ill patients often lack decision-making capacity, surrogate decision-makers are asked to assist in making these difficult decisions. A large body of research has documented problems with the process and outcomes of surrogate decision-making in ICUs, including frequent failure to discuss patients' values, provide emotional support, hold timely family meetings, or explain treatment options such as comfort-focused care.[14-18] Surrogates in ICUs perceive their role as challenging[19-21] and experience high levels of depression, anxiety, and PTSD.[22,23] There is also evidence that critically-ill patients often receive more intensive life-extending treatment than they would choose for themselves, which is problematic because of the impact on both individual patients and the costs of medical care near the end of life.[24,25]

Although the scope of problems with surrogate decision-making for critically ill patients is well-documented, there are few evidence-based strategies to improve patient, family, and health system outcomes in patients with advanced critical illness.

We therefore developed a multi-component intervention delivered by the interprofessional ICU team to provide structured support of families throughout the ICU stay.[26-28] The intervention is designed to follow to national recommendations to utilize interdisciplinary teams to support patients and families[29,30] and leverage nurses' professional orientation toward providing patient and family-centered care.[31,26-28] The present trial differs from a previous trial of a similar intervention in several important ways. First, compared to the prior intervention tested,[32] in the present trial, the scope of the PARNTER intervention was expanded to include a process to foster greater involvement of specialist Palliative Care clinicians into patients care and audit and feedback to be provided to each ICU. Second, the prior trial was completed with a small internal grant, which did not allow detailed collection of a variety of process outcomes, such as communication practices in both study arms and timing of decisions to limit the use of life-prolonging treatments or transition to comfort-focused goals of care. The present trial contains detailed data collection on these points. Third, the prior trial did not assess the impact of the intervention on bedside nurses which is included in the present trial's secondary outcomes. Herein we present the trial methodology, describe the study intervention, and discuss our approach to three key methodological challenges – determining level of randomization, integrating the intervention with existing clinical staff, and retaining participants in long-term follow-up.

METHODS

Overview of Trial Methodology

This is a pragmatic, stepped-wedge, cluster randomized controlled trial evaluating the PARTNER intervention compared to usual care control. We will assess the intervention's effect on three domains of outcomes: measures of the patient-centeredness of care and quality of clinician-family communication, surrogates' symptoms of long-term psychological distress, and healthcare utilization.

PARTNER Intervention Protocol

Trial Centers and Participants

The trial will be conducted in five ICUs at four hospitals in Pennsylvania within the UPMC Health System: three medical ICUs within three community hospitals in which intensivist physicians serve as the attending physician of record for all patients, and a cardiac ICU and cardiothoracic surgical ICU within one academic hospital, in which intensivist physicians provide care for all patients in collaboration with a primary attending physician.

The trial will include all patients in the study ICUs who meet eligibility criteria during the enrollment period. Detailed inclusion and exclusion criteria are summarized in Table 1 for patients, surrogate decision-makers and nurses. Inclusion criteria for patients includes an age of 21 years or greater, lack of decision making capacity, and at least one of the following: receipt of mechanical ventilation for at least four consecutive days, judgment by the attending physician that the patient has at least a 40% chance of death during the hospitalization or at least a 40% chance of severe long-term functional impairment. Daily a designed staff member in the ICU will screen the census and discuss each patient with the attending physician to determine eligibility for enrollment in the intervention pathway. Nurse-leaders will identify one surrogate decision-maker per patient whom the family identifies as the patient's main surrogate and research staff will obtain their verbal consent for long-term follow-up over the phone. Nurses will be eligible if they were full time staff nurses in the ICU during the study period.

The study will be overseen by an independent Data and Safety Monitoring Committee (DSMC) consisting of three members with collective expertise in biostatistics, health services research, critical care medicine, behavioral interventions, and bioethics. No interim analyses will be conducted. The DSMC will monitor patient accrual, retention, and adverse events using a prespecified adverse event reporting protocol. The DSMC is empowered to stop the trial if evidence emerges of unexpectedly high rates of adverse events related to the intervention. Protocol amendments will be made in consultation with the trial's DSMC and the funding agency.

Patient and Public Involvement

Patients and the public were not directly involved in the design, recruitment, or conduct of this study. However, research questions and outcomes measures were developed and informed by patients' and surrogates' priorities, experiences, and preferences.[14-18]

Description of the PARTNER Intervention

The PARTNER intervention is conceptually grounded in the Cognitive Emotional Decision Making (CEDM) framework and Ottawa Decision Support Framework (ODSF).[33,34] The CEDM framework views medical decisions as influenced by not only cognitive and informational considerations, but also the emotional distress that arises from witnessing a critically-ill loved one and being required to make difficult, highly consequential decisions for them. The ODSF conceives that better patient/family decision-making can be achieved by 1) identifying decision support needs; 2) providing tailored decision support and 3) evaluating the decision-making process and outcomes.[33,35]

The PARTNER intervention will be deployed at the level of individual ICUs and delivered by the existing interprofessional ICU team. It will be overseen by four to six nurses from each ICU called the PARTNER nurses, nominated by their ICU director because they were judged to possess strong communication

skills. The intervention entails guideline-recommended strategies for providing emotional support to surrogates and for ensuring frequent clinician–family communication.[31,36,37] The four main components, detailed below, are: 1) advanced communication skills training for 4-6 nurses from each ICU to deliver support to surrogates throughout the ICU stay; 2) deploying a structured family support pathway delivered by the interprofessional ICU team 3) enacting strategies to increase the timely consultation of palliative care clinicians when appropriate; and 4) providing comprehensive implementation support to ensure reliable delivery of the PARTNER intervention (Table 2.)

Advanced communication Skills Training for PARTNER nurses: PARTNER nurses from each ICU will participate as a group in a 12-hour standardized, skills-focused training to develop the skills needed to support the surrogates of patients with advanced critical illness, summarized in Table 2. The training program for the PARTNER nurses adheres to best practice recommendations from the NIH Behavior Change Consortium.[38] The teaching methods are grounded in principles of self-efficacy and adult learning theory[39] and include: didactic explanation of the skill; demonstration by an expert clinician; small group practice with experiences medical actors portraying families; and structured learner-centered feedback provided by an expert educator.

Deploying a structured family support pathway delivered by the interprofessional ICU team: After the nurses are trained in communication skills for the PARTNER intervention, each ICU will institute the family support pathway. The pathway involves the PARTNER nurses meeting with families daily, according to a standardized protocol, and arranging interdisciplinary clinician–family meetings within 48 hours after enrollment and every 5 to 7 days thereafter. In addition, the PARTNER nurses meet with families before and after each family meeting to prepare them for the meeting and to debrief after the meeting. They also huddle with the clinical team before each family meeting. The main objectives of each encounter are summarized in Table 2 and depicted in timeline format beginning from the day of enrollment in Figure 1.

The PARTNER intervention uses strategies from behavioral economics and implementation science to overcome barriers to achieving frequent, structured family meetings. For example, the intervention resets the care default regarding timing of family meetings by switching from an “opt-in” to an “opt-out” approach to scheduling. Specifically, the PARTNER nurses will schedule family meetings per protocol unless the attending physician takes active steps to override the protocol, rather than requiring the clinical team to take active steps to schedule family meetings.

Deploying strategies to increase collaboration between Specialist Palliative Care (PC) and Critical Care services: We will use three strategies: 1) identifying a specialist PC physician champion in each ICU to spearhead increased involvement of PC services; 2) facilitating a process in each ICU in which clinicians develop a set of suggested “triggers” for PC consultation;[40,41] and 3) conducting twice weekly, in-person meetings between ICU and PC teams to assess whether any patients receiving the PARTNER intervention may benefit from a specialist PC consultation.

Providing Comprehensive Implementation Support: The strategy for deployment is grounded in best practice recommendations to change clinician behavior and enact system-level interventions.[42] Our approach to implementation is informed by the theory of planned behavior, which holds that success is determined by the strength of providers’ motivation to engage and their perceived degree of control to implement the intervention, which is largely influenced by perceived self-efficacy and organizational factors.[43,44]

We will use five main techniques to encourage adherence throughout the study:

Engagement of hospital and ICU leadership: Prior to deployment at each site, study investigators will meet with hospital and ICU leadership to secure their endorsement of the PARTNER intervention. These leaders will send emails hospital-wide endorsing the intervention, as well as tailored emails to all ICU clinicians encouraging them to actively participate.

Identification of PARTNER champions: We will identify local nursing, critical care, and PC champions in each ICU. These individuals will take on a leadership role for promoting the intervention and assisting with implementation challenges.

Orientation of all staff to PARTNER intervention: We will provide ICU physicians and bedside nurses with a structured orientation to the new care model and PARTNER nurses' role responsibilities.

On-site implementation support: During the first two weeks of deployment, an implementation specialist will be on-site to provide daily assistance. Thereafter, the implementation specialist makes weekly visits to directly observe the clinicians deploying the intervention, provide feedback, and assist in overcoming implementation challenges.

Quarterly audit and feedback: The study team will provide each ICU with feedback on the extent to which the intervention is being deployed as planned with statistics summarizing the number of patients enrolled, proportion who received family meetings per protocol, frequency and timing of family meetings compared to control phase, and frequency and timing of PC consults compared to control phase.

Description of Usual Care Arm:

The control treatment consists of usual care. No study ICU has a protocolized approach to family communication or requires family meetings to be conducted at set times. At the time of the study, none of the ICUs will receive implementation support, audit, or feedback related to family support and communication. Palliative care consultation is available in all study ICUs.

Randomization

The unit of randomization is the individual ICU. Study statistician' used a computer generated randomization scheme to determine the order in which ICUs transition from the control phase to the intervention phase. Table 3 depicts randomization results with targeted timeline and accrual rates. The plan is to complete enrollment in April 2019 and long-term follow-up in September 2019. All ICUs will receive the intervention by the end of the study period.

Blinding

The study staff performing chart abstraction and telephone follow-up of participants to ascertain study outcomes will be blinded to participants' treatment-group assignment. The nature of the intervention made it infeasible to mask physicians and surrogates to the patients' treatment-group assignment.

Outcomes

We developed an outcome assessment strategy to measure the effect of the intervention on three interrelated issues: the quality of communication and patient- and-family centeredness of care processes, surrogates' long-term psychological distress, and healthcare utilization and costs (Table 4.)

The primary outcome measure is surrogates' total score on the Quality of Communication (QOC) scale, measured during telephone follow-up 6-months after patient's discharge from the index hospitalization. The Quality of Communication (QOC) Scale is a 13-item scale measuring quality of communication with good internal consistency, strong evidence of reliability and validity,[45,46] and established responsiveness to change.[47] The QOC scale is a patient and family-centered outcome because it measures aspects of care rated as highly important to patients and their families. Higher scores on the QOC scale have been associated with higher ratings of the patient centeredness of care,[48] more goal concordant care, and shorter duration of ICU care before death.[32,48] We decided to focus long-term follow-up on only one time point in order to minimize the burden on family members, many of whom will be recently bereaved, and also to stay within budgetary constraints. We selected the 6-month time point because the QOC has established responsiveness to change at 6-months,[32] and the secondary measures of psychological distress are of uncertain clinical significance prior to the 6-month time point.

The investigative team originally planned to use as the primary outcome surrogates' scores on the Hospital Anxiety and Depression Scale (HADS) at 6 months follow up. However, the primary outcome was revised to the QOC scale and updated within ClinicalTrials.gov on April 10, 2018. The change in primary outcome measure was made in consultation with the trial's DSMC and the funding agency. The decision was based entirely on new evidence external to the trial. At no time did investigators have access to outcome data from the trial, which will not be made available to investigators until the trial is complete.

The rationale for this change was accumulating evidence that the type of intervention tested in this trial (i.e., an intervention restricted to the ICU setting) is unlikely to improve surrogates' long-term symptoms of anxiety and depression. Two recently published RCTs of interventions focused on supporting family members acting as surrogates during their time in the ICU did not improve surrogates' psychological distress[32] and may have worsened symptoms of PTSD.[49] One of the interventions was very similar in design to the intervention being tested in the current trial.[32]

We will assess the following outcome measures through telephone interviews with surrogates at 6-month follow up:

Measures of Communication and Decision Quality:

Patient- and family-centeredness of care: measured with the Patient Perception of Patient Centeredness (PPPC) scale, modified for use by surrogates. The PPPC is a 12-item instrument that has established validity and reliability.[50,51]

Decisional regret: measured with the Decisional Regret Scale (DRS), a 5-item assessment of "distress or remorse after healthcare decisions." It has high internal consistency and convergent validity.[52]

Surrogates' Psychological Distress:

Anxiety and depressive symptoms: The Hospital Anxiety and Depression Scale (HADS) is a 14-item, two-domain instrument used to study anxiety and depression with established reliability and validity among ICU surrogates.[27,53-58]

Symptoms of post-traumatic stress disorder: The Impact of Events Scale (IES) is a 15-item tool measuring total stress with subscales for intrusiveness and avoidance.[59] It has been successfully used among ICU surrogates.[22,27]

Patients' Outcomes:

Discharge disposition: We will use UPMC administrative records to determine if patients were discharged to home, hospice, a skilled nursing facility, another acute care hospital, and a long-term acute care facility.

Mortality: We will assess mortality during the index hospitalization and through 6-month follow-up using hospital records, telephone interviews with surrogates at 6-month follow-up, and the Social Security Death Master File in cases if participants are lost to telephone follow-up.

Functional status at 6 months: We will assess patients' functional status at 6-months after discharge using the Katz ADL instrument completed by surrogates during the 6-month follow-up call.[60]

Healthcare Utilization and Costs:

ICU and hospital length of stay: We will determine the intervention's impact on patients' ICU and hospital length of stay, measured from study enrollment using the UPMC electronic medical record.

Total hospitalization costs: We will measure costs during the index hospitalization using the UPMC computerized cost accounting system, which assigns specific costs to each service based on hospital expenses. UPMC developed this activity-based costing (ABC) system to align costs with patients based on actual utilization of resources. Direct expenses, such as blood products, drugs, and supplies, are allocated on a patient-incurred basis. Departmental labor and other expenses are allocated to patients using specific cost drivers, such minutes on a nursing unit or time in an OR. This costing method excludes expenses related to physician margin (Physician Services Division Sweep and Support), Enterprise Shared Services, and other fully indirect expenses. These excluded categories total approximately 25% of total hospital expenses. Because this costing system excludes these fixed costs, the costs may alternatively be labelled "total controllable hospitalization costs". Further details of the activity-based costing system can be found at: https://www.healthcatalyst.com/success_stories/activitybased-costing-in-healthcare-service-lines-upmc. To calculate direct variable costs, we will remove the fixed costs of overhead that are not related to patient throughput, determined through individual departmental usage patterns and will aggregate each patient's total service specific costs.[61]

Healthcare utilization through 6-month follow up: We will measure healthcare utilization that occurs between index hospitalization discharge and 6-month follow up using an established method based on in-depth interview with the patient's surrogate during the 6-month follow-up call.[62] The interview contains questions to determine the number of post-discharge hospital admissions, nursing

home admissions, emergency department visits, physician visits, hospice use, and home health service utilization.

Cost of Implementing PARTNER Intervention: To calculate costs to implement the intervention, we will determine the cost of all training, inclusive of salary/fringe costs of nurses, actors, and instructors. We will also include costs related to ongoing implementation support during the intervention phase of the study, including the implementation specialists' time, mileage and parking for travel between sites.

Statistical Methods

All analyses will be performed on an intention-to-treat basis. The individual ICU is the unit of randomization and individual surrogate/patient is the unit of analysis. To compare surrogates' characteristics across treatment groups, we will use t-tests or Wilcoxon rank-sum tests for continuous outcomes and chi-square or Fisher's exact tests for categorical outcomes. To determine whether the intervention impacts QOC scores (as well as other continuous secondary outcomes), we will use generalized linear mixed model (GLMM) to account for temporal and clustering effects typically encountered in stepped-wedge clinical trial designs.[63,64] Clustering effects by ICU will be treated as random in the models. We will include time as fixed effects to account for secular trends over time and include time by treatment interaction to investigate whether treatment effect is time-varying. The model will also include random slopes of time to account for possible heterogeneous temporal effects across ICUs.

A known limitation of the stepped-wedge cluster RCT design is that there are often imbalances in patient characteristics across study sites that site-level randomization does not address. Therefore, it is an accepted strategy in stepped-wedge trials to pre-specify that certain co-variates will be adjusted for in the statistical analysis plan. We will therefore adjust analyses for patient age, modified SAPS III, Elixhauser index, mechanical ventilation usage, and admission source. In addition, if there are baseline differences between other demographic characteristics across treatment arms, we will adjust for those associated with the outcome in univariate analysis with a p-value less than or equal to 0.20. Should missing data prove problematic we will use the methods of multiple imputations or inverse probability weighting.[65] Final models will be assessed for stability using routine model diagnostics to identify potential outliers and/or influential observations.

Sample Size Determination. With a sample size of 690 surrogates, assuming 20% loss to follow-up and alpha=0.05, we will have 80% power to detect a small effect size difference (Cohen's d: 0.30) between groups on the QOC scale. The MCID for the QOC scale has not been established, but differences between groups of this magnitude were observed in a recent trial of a family support intervention in ICUs and were associated with improved ratings of patient- and family centeredness of care (measured with the modified Patient Perceptions of Patient-Centeredness scale), as well as a shortened ICU and hospital length of stay among dying patients.[66] In addition, a recent trial of an intervention to improve communication about goals of care yielded significant improvements in the QOC with a Cohen's d of 0.56, which were in turn associated with improved rating of goal-concordant care among patients with stable goals through 3-month follow-up.[67]

The power calculation was done via NCSS PASS 15 using the pooled outcome standard deviation (SD=24.5) and coefficient of variation (COV=0.15) from the Family-Support Intervention in Intensive Care Units study.[48] We assumed a two-sided alpha level of 0.05 and a conservative estimate of 20% for the rate of surrogate loss to follow-up.

The enrollment goal was initially 1,000 and changed to 690 after a senior biostatistician joined the study team. We re-examined initial power calculations and concluded we were over-powered for our main outcome measure and any gains from obtaining a larger sample size would be only incremental. For practical reasons, because of recent decreases in ICU admissions to UPMC hospitals due to a split between UPMC and Highmark, one of the main health insurance companies, we determined that enrollment would likely be slower than we originally predicted. Given the nature of stepped-wedge trials (i.e. control subjects enrolled first, then intervention subjects later) there was concern slow enrollment could led to a circumstance in which too few intervention patients are enrolled.

Ethics and Dissemination

Research Ethics Approval: The institutional review board of the University of Pittsburgh and the quality improvement committee of the UPMC Health System approved the project. The leadership of each participating ICU also approved the project. The intervention was judged to be a quality improvement initiative. Surrogates of eligible patients were informed of the QI project by ICU staff, however consent was not required for enrollment in the intervention pathway. The long-term follow-up of surrogates and nurses was judged to be research. Nurse-leaders within each ICU will identify a surrogate decision-maker and introduce the research study. If family members give permission for the research staff to contact them, forms will be faxed or emailed via secure server behind the institutional firewall to the research staff who then attempt to call within 48 hours. If the family member is willing to participate, we continue with the verbal consent process over the phone. Nurses will provide written informed consent for their participation. The trial was registered on ClinicalTrials.gov before enrollment commenced (NCT02445937). This work was supported by NIH/NINR grant number R01NR014663.

Dissemination: We will make results available to surrogate decision-makers and caregivers, the funders, critical care societies, and other researchers. We will use traditional methods, including presentation at national meetings, submission to peer reviewed journals, and use of social media to disseminate findings.

DISCUSSION

While planning the trial, we identified three key design and implementation challenges: 1) determining the optimal type of randomized trial design, 2) using existing clinical staff to deploy the intervention, and 3) maximizing long-term follow-up.

We chose to use a stepped-wedge cluster randomized design rather than an individual-level RCT or a cluster RCT for two main reasons. First, we judged that randomizing individual patients within ICUs would create a high risk of contamination of the control arm because the intervention is deployed at the

ICU-level. Second, a cluster RCT would involve randomly assigning half of the ICUs to receive the intervention and half to receive the control for the duration of the study. Individual ICUs were unwilling to be randomized to a control condition for the duration of the study because of mounting societal pressure to improve end-of-life care for patients with advanced critical illness. We ultimately selected a stepped-wedge cluster randomized design allows randomization at the ICU-level and allows all ICUs to receive the intervention during the study period.

We elected to use existing clinical staff to deploy the intervention for two main reasons. First, doing so increases the scalability of the intervention compared to either using research personnel to deliver the intervention to adding additional clinical personnel to the ICU care team to deliver the intervention. Second, we hypothesize that achieving durable improvements in family support will require changing ICUs' overall culture and processes of care, which may be more likely to occur when the intervention targets the entire interprofessional team rather than external interventionists.

Deploying the PARTNER intervention through the existing interprofessional team also presents several challenges. First, ICU clinicians are busy and the PARTNER intervention will likely result in an increase in the amount of time devoted to clinician-family communication. We address this by providing on-site support to develop efficient care processes and training multiple PARTNER nurses per unit. Second, few frontline clinicians have experience deploying complex, protocolized behavioral interventions, which may pose threats to intervention fidelity. We addressed the potential issue by developing a rigorous training program that focuses on the need for high adherence to protocol. In addition, we designed an extensive monitoring programming that involves weekly site visits with direct observation and coaching by implementation specialists, quarterly "booster" training sessions in which key communication skills are reviewed, and quarterly audit and feedback sessions where unit adherence is summarized.

The third challenge is achieving adequately high rates of long-term follow-up. Long-term follow-up can be challenging in this population because most of the participants will either be recently bereaved or will be caregivers for survivors of critical illness. We developed three strategies to maximize retention during the follow-up period. First, we collect extensive contact information at initial consenting including phone numbers, mailing addresses, and email addresses of both the patient's surrogate and an alternate contact who will know how to contact the participant if the surrogate's contact information is no longer valid. Second, we seek to maintain contact with the surrogate after hospital discharge beginning with a thank you note following the consenting process. We also send participants a letter 4-month post-hospitalization with information on scheduling the 6-month follow-up call at their convenience. Third, we developed a protocol for subjects who were hard-to-reach outlining appropriate use of retention strategies, such as voicemail, a hard-to-reach letter, mail return service requesting, use of the alternate contact, online searches for new information, and a version of the follow-up interview to complete via mail. We ensure these protocols are implemented through use of software with detailed record of all follow-up activities.

Table 1. Eligibility criteria

Patient	
Inclusion criteria	Age ≥21 years Lack of decision-making capacity as determined by the clinical examination of the attending physician At least one of the following: 1. ≥96hrs of mechanical ventilation 2. ≥40% chance of hospital mortality as judged by the patient's attending physician 3. ≥40% chance of severe long-term functional impairment as judged by the patient's attending physician
Exclusion criteria	Lack of surrogate decisions maker Imminent organ transplantation
Surrogate	
Inclusion criteria	Clinical surrogate decision-maker, identified as the person making decisions for the patient
Exclusion criteria	Age <18 years Unable to read and understand English Unable to cannot complete questionnaires due to physical or cognitive limitations
Clinician	
Inclusion criteria	PARTNER nurses (e.g. nurse leaders, social workers) Treating clinicians (e.g. bedside nurses)
Exclusion criteria	None

Table 2. Four Components of the PARTNER Intervention

1. Advanced Communication Skills Training for 4-6 Nurses From Each ICU to Deliver Support to Surrogates Throughout the ICU Stay	
Duration	12 hours
Teaching Methods	Didactic explanation of skills to be learned Demonstration of the skill by an expert clinician Small group practice with simulated families • Learners receive feedback from and observe each other interact with simulated families • Structured-learner centered feedback provided by an expert communication skills educator
Core Skills	Interacting with families: • Establishing emotional supportive relationships • Daily check-ins with the families to elicit questions or concerns and provide update on the plans for the day. • Preparing families for IDFM by explaining meeting goals, eliciting the patient's values, and helping them formulate their main question using a question prompt • Attending family meetings to emotionally support the family and, if needed, use prompting skills to ensure that the families' main questions are addressed. Interacting with providers: • Conveying family questions and concerns to providers before IDFMS • Verbal prompting and persuasion to ensure structured, regular clinician-family communication • Ensuring care coordination when new clinicians come on service Documenting family meetings
Ongoing training	Quarterly "booster" training sessions in which key skills are reviewed and practiced
2. Deploying a Structured Family Support Pathway Delivered by Interprofessional ICU Team	
First Meeting with Family	Performs introduction Provides emotional support using NURSE behaviors Gets to know the family and the patient as individuals Orients the family to the ICU
Before Interdisciplinary Meeting with Family	Provides emotional support Explains what to expect in the meeting Elicits main concerns and completes question prompt list
Interdisciplinary Meeting with Family	Provides emotional support Ensures that the family's main questions are answered Brings the conversation back to the patient as an individual

	Ensures that the treatment options are discussed Ensures that there is a clear follow-up plan
After Interdisciplinary Meeting with the Family	Attends to emotions raised during the meeting Elicits questions Corrects any misunderstandings of issues addressed during the meeting
Daily Check-In	Check in daily to see how the family is doing Updates the family on the plan for the day Provides emotional support Elicits questions and concerns

3. Enacting Strategies to Increase Collaboration between ICU and Palliative Care Services

	Establishing a "Palliative Care Champion" Provision of recommended "triggers"† for PC consultation Twice weekly, in-person meetings between PC and ICU services to review the ICU census

4. Providing Comprehensive Implementation Support to Deploy the Intervention in Each ICU

Engagement of Hospital and ICU Leadership	Prior to implementation, study investigators sought explicit endorsement of the PARTNER program from hospital and ICU leadership at each site.
Recruitment of PARTNER Physician and Nurse Champions	We will identify local nurse and critical care physician leaders at each site to act as a champion. These individuals commit to taking a leadership role for promoting the intervention and assisting with implementation challenges.
Orientation of All Staff to the Intervention	Study investigators will provide ICU physicians and bedside nurses with a structured orientation to the new care model and PARTNER nurses' role responsibilities via email communications and in-person education sessions.
On-site Implementation Support	During the first two weeks of deployment, an implementation specialist is on-site to provide daily assistance. Thereafter, the implementation specialist makes weekly visits to directly observe the clinicians deploying the intervention, provide feedback, and assist in overcoming implementation challenges.
Quarterly Audit and Feedback	Audit-generated feedback on site performance of key process measures: number of patients enrolled, proportion who received IDFMs per protocol, frequency and timing of IDFMs compared to control phase, and frequency and timing of PC consults compared to control phase

[PARNTER - Pairing Re-engineered ICU Team with Nurse-driven Emotional Support and Relationship-building, ICU – intensive care unit, IDFM – Interdisciplinary Family Meeting.]

*Evidence-based strategies include the skills summarized in the NURSE mnemonic[68]

†Proposed by expert working group, as summarized by Weissman and Meier[40] and a suggested consensus-building strategy from the IPAL-ICU working group.[41]

Figure 1. Family Interaction with the PARTNER Nurse in the Family-Support Pathway

Timeline depicting each encounter between the PARTNER Nurse and families in the Family-Support Pathway beginning from the day of enrollment, noted as day 1.

Table 3. Randomization results and the order of sites shifting to intervention phase with target timeline and accrual.

Site	2015				2016				2017				2018			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
	CONTROL				INTERVENTION											
Community Hospital 1 MICU	Target=23				Target=115											
Community Hospital 2 MICU	Target=46							Target=92								
Academic Hospital CTICU	Target=69								Target=69							
Community Hospital 3 MICU	Target=92										Target=46					
Academic Hospital CCU	Target=115												Target= 23			

Table 4. Outcomes

Domain	Outcomes	Instrument Used	Data Source	Timing of measurement
Surrogate Decision Maker Outcome				
Measures of Communication and Decision Quality	Quality of communication	Quality of Communication Scale (QOC) [§]	Survey	6-month follow-up from enrollment
	Patient-centeredness of care	Patient Perception of Patient Centeredness (PPPC)[‡] scale, modified for use by surrogates. The	Survey	6-month follow-up from enrollment
	Decisional regret	Decisional Regret Scale (DRS)	Survey	6-month follow-up from enrollment

Psychological Symptoms Burden	Anxiety and depression	Hospital Anxiety and Depression Score (HADS) *	Survey	6-month follow-up from enrollment
	Post-traumatic stress	Impact of Events Scale (IES) †	Survey	6-month follow-up from enrollment
Healthcare Costs				
Payer Perspective	Index hospitalization cost		Hospital billing records	Post-discharge
	Post-discharge health care utilization		Hospital billing records, medical records and surrogate interview	6-month follow-up from enrollment
	Hospital readmission rates		Surrogate	6-month follow-up from enrollment
Hospital Perspective	Index hospitalization costs		UPMC health systems' Computerized cost accounting system	Post-discharge
	ICU and hospital length of stay		Registration data, chart abstraction	Post-discharge
	Intervention costs		Administrative records of cost of training and follow-up (salary costs, training, costs, and costs to supervise and deploy the intervention)	Post-discharge
Patient-Centered Outcomes				
	Discharge disposition (including in hospital mortality)		Registration data, chart abstraction	Post-discharge
	Functional status at 6 months	Katz ADL¶	Surrogate	6-month follow-up from enrollment
	Living situation at 6 months		6-month follow-up with surrogates	6-month follow-up from enrollment

	All-cause 6-month mortality		Hospital records, 6-month follow-up with surrogates, and the National Death Index	6-month follow-up from enrollment
Clinician Outcomes				
	Clinician burnout	Maslach Burnout Inventory**	Bedside nurses caring for patients enrolled in the study	Baseline, 6-month after randomization
Process Measures				
	Frequency of multidisciplinary communication		Chart abstraction	Post-discharge
	Palliative care and ethics consultations		Chart abstraction	Post-discharge
	Social work involvement		Chart abstraction	Post-discharge
	Pastoral care involvement		Chart abstraction	Post-discharge
	Incidence and timing of life support decisions		Chart abstraction	Post-discharge

*HADS is a 14-item assessment with subscales for anxiety and depression. Each domain has a score range of 0-21 with the following interpretation: 0-7 normal, 8-10 borderline abnormal, and 11-21, abnormal.

†IES is a 15-item tool measuring total stress (score range of 0-75) with subscales for intrusiveness (score range 0-35) and avoidance (score range 0-40). Total stress score is interpreted as follows: 0-8 subclinical range, 9-25 mild range, 26-43 moderate range, and 44 severe range. A score of ≥30 indicates a high risk of post-traumatic stress disorder (PTSD). The IES is a valid, reliable, and responsive 15-item instrument measuring symptoms of avoidance and intrusive thoughts.[59] It has been successfully used among ICU surrogates.[22,27]

‡PPPC is a 12-item instrument that measures the patient-centeredness of care and has demonstrated validity and reliability when used by surrogates. (Cronbach's $\alpha = 0.71$)[50] A recent systematic review found the PPPC to be one of two best instruments to measur this construct.[51]

§QOC is a 13-item scale measuring quality of communication with good internal consistency (alpha = 0.94), strong evidence of reliability and validity[45,46] and established responsiveness to change.[47] The total score ranges from 0-100, with neither floor (0) nor ceiling (100) effects.

DRS is a 5-item assessment of "distress or remorse after healthcare decisions." It has high internal consistency and convergent validity.[69]

¶ Katz ADL

** Maslach Burnout Inventory is a validated, widely used measure of clinician burnout.[70-72]

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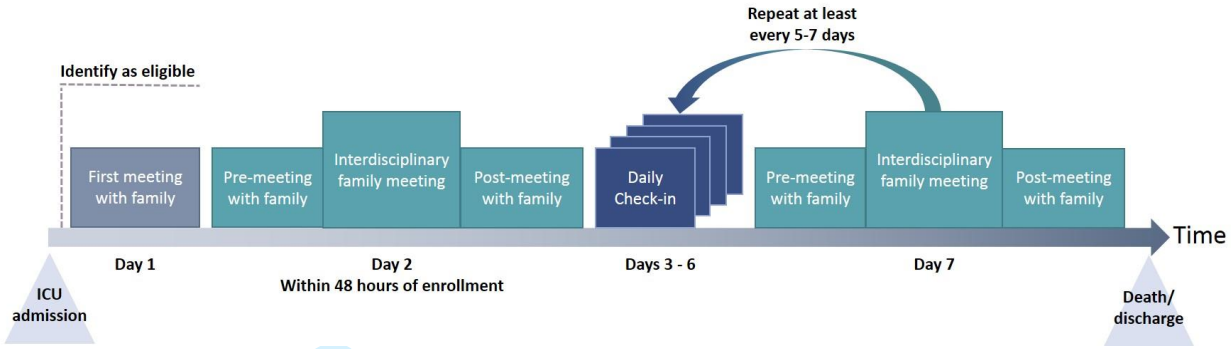
Figure 1. Family Interaction with the PARTNER Nurse in the Family-Support Pathway



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	4

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4, Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4-6, Table 2, Fig.1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5-6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9, Table 4
Participant timeline	13	Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig. 1, Table 3

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9-10
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7, 4, 10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-9, Table 4
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10, 11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	N/A
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9, 10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	4
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	4
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	4
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	4
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	4

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4, 10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	N/A
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	22
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.