PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a Randomized Trial of an Interprofessional Team-delivered Intervention to Support Surrogate Decision Makers in ICUs
AUTHORS	Lincoln, Taylor; Shields, Anne-Marie; Buddadhumaruk, Praewpannarai; Chang, Chung-Chou H.; Pike, Francis; Chen, Hsiang-Yu; Brown, Elke; Kozar, Veronica; Pidro, Caroline; Kahn, Jeremy M.; Darby, Joseph; Martin, Susan; Angus, Derek C; Arnold, Robert M; White, Douglas B

VERSION 1 – REVIEW

REVIEWER	Margaret Schwarze University of Wisconsin-Madison
REVIEW RETURNED	11-Sep-2019

GENERAL COMMENTS	I have been asked to review “Protocol for a Randomized Trial of an Interprofessional Team-delivered Intervention to Support Surrogate Decision Makers in ICUs” BMJOPEN-2019-033521. This protocol paper describes a randomized clinical trial using a stepped wedge design at 5 ICUs of an intervention aimed at improving clinician-surrogate communication through the use of nurse training, planned family meetings, increased access to palliative care and enhanced implementation support for these 3 items. The primary outcome of this study is Quality of Communication as reported by enrolled surrogates at 6 months after ICU admission for patients with very serious illness. This is an important study and the paper is well-written. However, in its current form there are several missing items and related concerns that make it unsuitable for publication. 1. The BMJ format and instructions note that this presentation is for planned or ongoing studies, yet the timeline included on page 23 suggests this study was completed (or aimed for completion) on June 30, 2018. 2. The authors have published the results of a very similar intervention in NEJM, May 23, 2018. It would help this manuscript greatly to explicitly describe this other study (not just reference it) and explain how the intervention herein (and this study) differ, as this protocol seems very nearly identical with a few exceptions. If there are only small differences then the authors need to clarify why these differences are important and a second trial is necessary. 3. The authors note the primary outcome is QOC at 6 months. This seems very far downstream from the event and potentially subject to high recall bias. It would be helpful to understand why this timeframe was chosen and why there is confidence that this measurement assessed at 6 months is clearly related to the intervention received.

	4. The authors note they obtain consent from surrogates for survey completion but the intervention is approved as QI. On page 8 the figure describes the intervention as occurring on day 2 or within 48 hours of enrollment. In addition, enrollment criteria include receipt of mechanical ventilation for at least 4 consecutive days, and 40% mortality or severe functional morbidity. All of this is very confusing. When are surrogates enrolled? How are they enrolled as this is a group who are typically very challenging to enroll in the ICU? When is the intervention applied and how is it confirmed that the patient's surrogate is eligible at 48 hours if that is not enough time to assess eligibility criteria. I suspect all of this somehow makes sense but the way it is described and the figures employed to assist the reader simply add to the confusion. Clear details on this point would be quite helpful to other researchers. 5. The authors are using a RCT study design but then propose adjusting for age, SAPS III, comorbidities and treatments received. Is the randomization doing anything if these adjustments are needed? Shouldn't these items be accounted for by the randomization process? With site as the level/unit of randomization, and only 5 sites, one would conclude that the between-site variation estimates are low, in order to perceive even a large effect. I am struggling to reconcile the need to reduce between-site variability by adjusting for patient differences and the notion that between site variability is low enough to have the power needed to perceive a small to medium effect. It seems quite important to explain the rationale behind the sample size and how assumptions about between site variation will be integrated into the analysis a bit more. Presently this seems like 5 pre/post studies with adjustments. 6. The date when the primary outcome was switched from HADS to QOC, and registered at CT.gov needs to be clearly described and a stronger explanation relating to the original PARTNER study should be provided. Studying clinician-patient communication is fraught with hazard in measurement, particularly picking a "primary" outcome. While the authors have provided some explanation for this, it seems a bit superficial and more related to the findings of their other study than the rationale they provide. Furthermore, there are examples of other "interventions related to the ICU setting and delivered by the intraprofessional ICU team" that have shown efficacy in changing the psychologic impact of the experience in the ICU (see Alzoulay, NEJM, 2007). More transparency about these measurement problems and the timing of these changes would be helpful to readers. Also, an explanation about why the enrollment goal was changed from 1000 to 690 is needed. 7. No funding source is noted. Although the study is clearly supported by UPMC for its QI efforts, what is the funding source for study design, data collection and analysis?

REVIEWER	Victoria Shepherd Cardiff University Cardiff UK
REVIEW RETURNED	07-Nov-2019

GENERAL COMMENTS	The protocol presents on a topic that is important and of great relevance to clinicians and patients and their families alike, since communication and decision-making in critical care is a major issue. Overall the protocol is well written, and the study is likely to make a useful contribution to the existing evidence on enhancing

	communication and decision-making processes in critical care. However, there are a few details which require minor revisions. My comments on the manuscript: General comments The tenses used vary throughout the protocol from future to present to past. Such as in Methods (Trial Centers and Participants) 'The trial is being conducted in five ICUs at four hospitals ….' 'The study will be overseen by an independent Data and Safety Monitoring Committee ..'. Greater consistency would be preferable where possible. SPIRIT checklist There appear to be a number of items missing from the checklist, including the role of the study sponsor and funder, composition of the oversight committees, data management etc. Further details should be added to the protocol manuscript and SPIRIT checklist. Methods Description of the PARTNER Intervention P.5 Line 50 the acronym 'PC' is not explained in full Outcomes P.7 Line 31 reports the change to the primary outcome (surrogates HADs score at 6 months). Further detail on when the primary outcome was changed is needed (prior to data collection or part way through? If so, at what point?).

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

I have been asked to review "Protocol for a Randomized Trial of an Interprofessional Team-delivered Intervention to Support Surrogate Decision Makers in ICUs" BMJOPEN-2019-033521. This protocol paper describes a randomized clinical trial using a stepped wedge design at 5 ICUs of an intervention aimed at improving clinician-surrogate communication through the use of nurse training, planned family meetings, increased access to palliative care and enhanced implementation support for these 3 items. The primary outcome of this study is Quality of Communication as reported by enrolled surrogates at 6 months after ICU admission for patients with very serious illness. This is an important study and the paper is well-written. However, in its current form there are several missing items and related concerns that make it unsuitable for publication.

Comment R1.1: The BMJ format and instructions note that this presentation is for planned or ongoing studies, yet the timeline included on page 23 suggests this study was completed (or aimed for completion) on June 30, 2018.

Response R1.1: We submitted the manuscript in August 2019 when study activities were ongoing. The timeline depicts randomization results with targeted timeline and accrual rates estimated

during the planning phases of the study. Ultimately, long-term follow-up was completed in September 2019.

Comment R1.2: The authors have published the results of a very similar intervention in NEJM, May 23, 2018. It would help this manuscript greatly to explicitly describe this other study (not just reference it) and explain how the intervention herein (and this study) differ, as this protocol seems very nearly identical with a few exceptions. If there are only small differences then the authors need to clarify why these differences are important and a second trial is necessary.

Response R1.2: Thank you for this suggestion. The first study was done with internal funding that did not allow for robust data collection in terms of a process evaluation of the intervention's impact on communication processes and decisions around forgoing life support, nor was it possible to study nurses' outcomes related to the intervention. Additionally, this iteration of the intervention included strategies to increase collaboration between Palliative Care and ICU services. We have included a similar description within the manuscript.

Comment R1.3: The authors note the primary outcome is QOC at 6-months. This seems very far downstream from the event and potentially subject to high recall bias. It would be helpful to understand why this timeframe was chosen and why there is confidence that this measurement assessed at 6 months is clearly related to the intervention received.

Response R1.3: We expanded the section on the primary outcomes to include justification for the 6-month time interval.

Comment R1.4: The authors note they obtain consent from surrogates for survey completion but the intervention is approved as QI. On page 8 the figure describes the intervention as occurring on day 2 or within 48 hours of enrollment. In addition, enrollment criteria include receipt of mechanical ventilation for at least 4 consecutive days, and 40% mortality or severe functional morbidity. All of this is very confusing. When are surrogates enrolled? How are they enrolled as this is a group who are typically very challenging to enroll in the ICU? When is the intervention applied and how is it confirmed that the patient's surrogate is eligible at 48 hours if that is not enough time to assess eligibility criteria. I suspect all of this somehow makes sense but the way it is described and the figures employed to assist the reader simply add to the confusion. Clear details on this point would be quite helpful to other researchers.

Response R1.4: Thank you bringing this section to our attention. Figure 1 depicts the encounters between the PARTNER nurse and the surrogate beginning from the time of enrollment, not the time of admission to the ICU. So, "day 2" is meant to indicate the second day from time of enrollment. We attempted to clarify this distinction by altering the language where the figure is mentioned in the text.

Patients are deemed eligible for enrollment in the intervention when they are found to meet enrollment criteria. Nurse-leaders then identify a surrogate decision-maker and ask permission for surrogates to participate in data collection. If the family member gives permission to be contacted about the data collection portion of the project, our research staff will call to obtain verbal consent prior to the conduct of the long-term follow-up. If the family member is willing to participate, we continue with the verbal consent process. Based on your feedback, this was clarified within the Trial Centers and Participants section on page 4 and the Ethics and Dissemination Section on page 10.

Comment R1.5: The authors are using a RCT study design but then propose adjusting for age, SAPS III, comorbidities and treatments received. Is the randomization doing anything if these adjustments are needed? Shouldn't these items be accounted for by the randomization process? With site as the level/unit of randomization, and only 5 sites, one would conclude that the between-site variation estimates are low, in order to perceive even a large effect. I am struggling to reconcile the need to reduce between-site variability by adjusting for patient differences and the notion that between site variability is low enough to have the power needed to perceive a small to medium effect. It seems quite important to explain the rationale behind the sample size and how assumptions about between site variation will be integrated into the analysis a bit more. Presently this seems like 5 pre/post studies with adjustments.

Response R1.5: Thank you. We included further justification within the Statistical Methods section on page 9.

Comment R1.6: The date when the primary outcome was switched from HADS to QOC, and registered at CT.gov needs to be clearly described and a stronger explanation relating to the original PARTNER study should be provided. Studying clinician-patient communication is fraught with hazard in measurement, particularly picking a "primary" outcome. While the authors have provided some explanation for this, it seems a bit superficial and more related to the findings of their other study than the rationale they provide. Furthermore, there are examples of other "interventions related to the ICU setting and delivered by the intraprofessional ICU team" that have shown efficacy in changing the psychologic impact of the experience in the ICU (see Alzoulay, NEJM, 2007). More transparency about these measurement problems and the timing of these changes would be helpful to readers. Also, an explanation about why the enrollment goal was changed from 1000 to 690 is needed.

Response R1.6:

The primary outcome was switched and updated within ClinicalTrials.gov on April 10, 2018. Based on your feedback, we have strengthened our explanation relating to the prior studies that influenced the decision within the Outcomes section.

Regarding the enrollment goal, a senior biostatistician joined the study team (Joyce Chang, PhD) and after examining our original power calculations concluded we are over-powered for our main outcome measure and any gains from obtaining a larger sample size will 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) slow enrollment could led to a circumstance in which too few intervention patients are enrolled. With 690 patients, and conservatively assuming 25% drop-out, we will have 80% power to detect changes as small as the MCID on the primary outcome measure (HADS). Specifically, we can detect 0.03-0.12 standard deviation in the outcome measure with > 80% power depending on rho. Being most conservative, we can detect differences as low as 0.12 SD or 0.5 units in the HADS score if SD=5.

Comment R1.7: No funding source is noted. Although the study is clearly supported by UPMC for its QI efforts, what is the funding source for study design, data collection and analysis?

Response R1.7: Thank you for the careful read. The funding source was mistakenly excluded. This has been corrected.

Reviewer: 2

The protocol presents on a topic that is important and of great relevance to clinicians and patients and their families alike, since communication and decision-making in critical care is a major issue. Overall the protocol is well written, and the study is likely to make a useful contribution to the existing evidence on enhancing communication and decision-making processes in critical care. However, there are a few details which require minor revisions. My comments on the manuscript:

General comments

Comment R2.1: The tenses used vary throughout the protocol from future to present to past. Such as in Methods (Trial Centers and Participants) 'The trial is being conducted in five ICUs at four hospitals ….' 'The study will be overseen by an independent Data and Safety Monitoring Committee ..'. Greater consistency would be preferable where possible.

Response R2.1: Thank you for the careful read, this has been corrected.

Comment R2.2: SPIRIT checklist

There appear to be a number of items missing from the checklist, including the role of the study sponsor and funder, composition of the oversight committees, data management etc. Further details should be added to the protocol manuscript and SPIRIT checklist.

Response R2.2: Thank you for the careful read, the SPIRIT checklist has been updated.

Comment R2.3: Methods

Description of the PARTNER Intervention

P.5 Line 50 the acronym 'PC' is not explained in full

Response R2.3: Thank you for the careful read, this has been corrected.

Comment R2.4: Outcomes

P.7 Line 31 reports the change to the primary outcome (surrogates HADs score at 6 months). Further detail on when the primary outcome was changed is needed (prior to data collection or part way through? If so, at what point?).

Response R2.4: Based on your feedback, we have strengthened our explanation relating to the prior studies that influenced the decision within the Outcomes section.

VERSION 2 – REVIEW

REVIEWER	Dr Victoria Shepherd Cardiff University, UK
REVIEW RETURNED	08-Jan-2020

GENERAL COMMENTS	Thank you for your careful revision of your manuscript 'Protocol for a Randomized Trial of an Interprofessional Team-delivered Intervention to Support Surrogate Decision Makers in ICUs.' The revised manuscript has addressed the issues raised. I note that the SPIRIT checklist is now complete. The authors commented in their response that consent forms for surrogate and nurse participation were submitted as supplementary files, however I have not able to find/access them amongst the supplementary files. I am happy to recommend acceptance of the manuscript, but note one small typographical error on p.6 line 42 where 'Study statistician'' should be amended.