# A randomized controlled trial on the efficacy of advance care planning on the quality of end-of-life care and communication in patients with COPD: the research protocol

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# A randomized controlled trial on the efficacy of advance care planning on the quality of end-of-life care and communication in patients with COPD: the research protocol

Carmen H.M. Houben[1], Martijn A. Spruit[1], Emiel F.M. Wouters[1,2] and Daisy J.A. Janssen[1, 3]

**Affiliations:** 1. Program Development Centre, CIRO+, centre of expertise for chronic organ failure, Horn, The Netherlands; 2. Respiratory Medicine, Maastricht UMC+, Maastricht, The Netherlands; 3. Centre of expertise for palliative care, Maastricht UMC+, Maastricht, The Netherlands.

**Address of correspondence:** Carmen H.M. Houben, MSc., Program Development Centre, Centre of Expertise for Chronic Organ Failure (CIRO+), Hornerheide 1, 6085 NM Horn, The Netherlands. E-mail: carmenhouben@ciro-horn.nl

**Key words:** Advance care planning, end-of-life care, palliative care, COPD

**ABSTRACT**

**Introduction:** Recent research shows that advance care planning (ACP) for patients with Chronic Obstructive Pulmonary Disease (COPD) is uncommon and poorly done. Aim of the present study is to explore whether and to what extent structured ACP by a trained nurse, in collaboration with the chest physician, can improve outcomes in Dutch patients with COPD and their family.

**Methods and analysis:** A multicentre cluster-randomized controlled trial in patients with COPD who are recently discharged after an exacerbation has been designed. Patients will be recruited from three Dutch hospitals and will be assigned to an intervention or control group, depending on the randomization of their chest physician. Patients will be assessed at baseline and after six and 12 months. The intervention group will receive a structured ACP session by a trained nurse. Primary outcomes are quality of communication about end-of-life care, symptoms of anxiety and depression, quality of end-of-life care, and quality of dying. Secondary outcomes include concordance between patient's preferences for end-of-life care and received end-of-life care, and psychological distress in bereaved family members of deceased patients. Intervention and control groups will be compared using univariate analyses and clustered regression analysis.

**Ethics and dissemination:** Ethical approval was received from the Medical Ethical Committee of the Catharina Hospital Eindhoven, The Netherlands (NL42437.060.12). The current project provides recommendations for guidelines on palliative care in COPD and supports implementation of ACP in regular clinical care.

**Clinical trial registration number:** NTR3940.

## ARTICLE SUMMARY

### Article focus

- This article describes the study protocol of a multicentre, prospective, cluster-randomized controlled trial on the influence of structured advance care planning (ACP) on quality of end-of-life care communication and quality of end-of-life care in Dutch patients with COPD.

### Key messages

- Primary outcomes are quality of communication about end-of-life care, symptoms of anxiety and depression, quality of end-of-life care, and quality of dying.
- Secondary outcomes include concordance between patient's preferences for end-of-life care and received end-of-life care, and psychological distress in bereaved family members of deceased patients with COPD.
- The study will include patients with severe to very severe COPD and their families.

### Strengths and limitations of this study

- The present study is a large, adequately powered, multicentre randomized controlled trial to investigate the effects of ACP in patients with (very) severe COPD.
- The results from this study will help to implement ACP in regular clinical care and will provide recommendations for guidelines on palliative care in COPD.
- Quality of end-of-life care and dying will be assessed subjectively and retrospectively. Therefore we will use well validated instruments to overcome this limitation.
- The current intervention consists of one single intervention, whereas ACP is an on-going process of communication. However, with this intervention we aimed to facilitate this continuous process between patients, families and physicians.

## INTRODUCTION

Advance care planning (ACP) provides patients with an opportunity to plan their future care, should they become incapable of participating in medical treatment decisions. These discussions can result into documentation of end-of-life care preferences in an advance directive[1]. However, ACP is not limited to the completion of advance directives. ACP is an on-going process in which patients, together with health care professionals and loved ones, discuss topics such as goals of care, resuscitation and life support, palliative care options, and surrogate decision making [2].

Previous studies have shown that ACP increases the occurrence of discussions about ACP[3 4], improves concordance between patient's preferences and end-of-life care received[5-7], and improves quality of care at the end-of-life[8] in different adult populations. Despite the fact that chronic obstructive pulmonary disease (COPD) is a leading cause of mortality worldwide[9] and unexpected deaths occur frequently[10], ACP studies are rarely focused on patients with COPD. A prospective cross-sectional study showed that outpatients with COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage III or IV are able to discuss preferences about life-sustaining treatments and are willing to discuss end-of-life care preferences. However, discussions about end-of-life care are rare and patients rated the quality of patient-physician communication about end-of-life care as poor[11]. The most common endorsed barriers for end-of-life care communication reported by physicians are lack of time, anxiety to take away patient's hope, and the assumption that the patient is not ready to talk about end-of-life care[12].

Although patients often prefer doctors to discuss ACP, they also accept other healthcare professionals as sources of ACP information. Nurses, for example, have specific skills that may facilitate communication about end-of-life care. They can provide prognostic information and support patients' hopes by understanding individual aspects of hope, focusing on patient's quality of life, and building trust with patients[13].

However, to date it remains unknown whether and to what extent structured ACP by a trained nurse in collaboration with the chest physician can improve outcomes in Dutch patients with COPD and their family. Therefore we have designed a cluster-randomized controlled trial on the efficacy of structured advance care planning on quality of end-of-life care communication and quality of end-of-life care in Dutch patients with COPD. The current manuscript describes the research protocol and provides an outline of possible strengths, weaknesses and clinical consequences.

**Hypothesis to be examined in the study**

We hypothesize that structured ACP by a trained nurse, in collaboration with the patient's physician, can improve quality of end-of-life care communication, as well as quality of end-of-life care and quality of dying for patients with COPD. In addition, we hypothesize that structured ACP won't result in increased symptoms of anxiety or depression.

**METHODS AND ANALYSIS**

**Study design**

A multicentre, cluster- randomized controlled trial has been designed. Patients with COPD who were recently discharged after an exacerbation will be recruited in an academic hospital and two general hospitals in the Netherlands. Patients in the intervention group will receive an ACP intervention within four weeks after discharge. The control group will receive usual care. The intervention and control group will be assessed at baseline and six and 12 months after enrolment (Figure 1).

**Eligibility criteria**

Eligible patients are those who satisfy all of the following criteria:

1. A diagnosis of severe to very severe COPD (GOLD grade III or IV)[14].
2. Discharged after hospital admission for a COPD exacerbation.

3. At least one loved one, who will participate in the study.

Patients will be excluded if they are unable to complete the questionnaires because of cognitive impairment or if they are unable to speak or understand Dutch.

**Intervention**

Respiratory nurse specialists will receive a two-day training to be able to perform the intervention. The training will consist of theory about the importance and benefits of ACP for patients with COPD and their loved ones. End-of-life care communication skills and the structured ACP session during the study will be taught and practiced. Participants will be asked to perform ACP with a standardized patient. Investigators will use a checklist to confirm adherence to the standardized protocol for ACP and provide certification if participants have achieve competency.

Certified respiratory nurse specialists will provide the structured ACP session in the patient's home environment in the presence of the patient and his or her loved one(s) within 4 weeks after discharge. The session will be prepared with the chest physician in advance. The structured ACP session will pay attention to several elements (Table 1). The content will be adapted to the patient's needs. The duration will be about 1.5 hours. Respiratory nurse specialists will be supervised by the research project team regularly to guarantee the quality of the structured ACP session.

As part of the structured ACP session, the respiratory nurse specialists will complete, together with the patient, a feedback form showing patient's: general goals of care; preferences for life-sustaining treatments (cardiopulmonary resuscitation, non-invasive positive pressure ventilation, and mechanical ventilation); and questions and concerns regarding end-of-life care. This feedback form will be provided to the patient, the chest physician and the general practitioner. Finally, patients will receive a brochure about palliative care for patients with COPD. This brochure is based on the Dutch guideline "palliative care for patients with COPD" and was developed for patients and their loved ones by the Lung Foundation Netherlands.

**Outcomes**

The following variables will be recorded during home visits at baseline and after six months in patients in the intervention and usual care group: demographics (including age, sex, educational level, religion); smoking history; medical history; current medication; post-bronchodilator Forced Expiratory Volume in the first second ($FEV_1$); use of long-term oxygen therapy; and use of non-invasive positive pressure ventilation.

*Primary outcomes*

Primary outcomes for all patients are:

- Quality of communication about end-of-life care (Quality of Communication (QOC))[15];
- Symptoms of anxiety and depression (Hospital Anxiety and Depression Scale (HADS))[16];

For patients who died during the study period, primary outcomes are:

- Quality of end-of-life care (Toolkit After-Death Bereaved Family Member Interview)[17];
- Quality of death and dying (Quality of Death and Dying (QODD))[18].

*Secondary outcomes*

Secondary outcomes are:

- Concordance between patient's preferences for end-of-life care (patient's preferences for cardiopulmonary resuscitation (CPR) and mechanical ventilation; End-of-life Preferences Interview (ELPI)[19] and received end-of-life care (life-sustaining treatment before dying; Toolkit After-Death Bereaved Family Member Interview)[17];
- Psychological distress in bereaved family members of deceased patients with COPD (HADS[16]; Inventory of Complicated Grief (ICG)[20]).

Patients in the intervention and usual care group will receive a phone call 12 months after enrolment to assess survival state. If the patient cannot be reached, the participating family

members will be contacted. If the patient deceased during the study period, a bereavement interview will be conducted with the participating family members. The following outcomes will be assessed: QODD[18]; Toolkit After-Death Bereaved Family Member Interview[17] ;ICG[20] ; and HADS[16].

Questionnaires that were not available in Dutch (QOC, ELPI, and Toolkit After-Death Bereaved Family Member Interview) have been translated into Dutch using a forward-backward translation procedure.

**Sample size**

A sample size calculation with a level of significance of 5% and a power of 90% has shown that 53 patients per group are needed in order to detect a difference of 1.0 point change in QOC end-of-life care domain score (standard deviation (SD) estimated as 2.53 points)[15] between the intervention and control group. A sample size calculation with a level of significance of 5% and power of 90% has shown that 32 deceased patients per group are needed in order to detect a difference of 10 points change in QODD scores between the intervention and control group. Since we expect a mortality rate within one year of about 23% and a dropout rate of about 10% because of other reasons, we will include 150 patients per group.

**Recruitment and randomization**

Patients will be informed about the study during their hospital admission for a COPD exacerbation. After discharge, the potential subject will receive a phone call. If the patient wants to participate an appointment for a first home visit will be made. Informed consent will be obtained at the start of this visit. Each subject will be assigned a study identification number. A list with identification codes linking the subject's names to subject's identification numbers will be stored in a limited access space.

Chest physicians of participating hospitals will be randomized into an intervention or usual care group using sealed opaque envelopes. We will cluster for chest physician to prevent cross-

contamination between the intervention and usual care group. Participating patients and their family members will receive the intervention or usual care, depending on the randomization of their chest physician. The researcher who will visit and phone the participants will not offer ACP.

**Data management and statistical analysis**

The data will be screened for outliers and missing values. These values will be excluded by list wise deletion. Missing data will be minimized because patients will be visited at home for completing the questionnaires and the researcher will check if all the questions have been answered. The study variables will be tested for normality. Demographic variables (such as age, sex, educational level, religion, and smoking history) will be compared between patients in the intervention group and control group, using independent-samples T-tests or Mann-Whitney U-tests, as appropriate, for continuous variables and Chi-square tests for categorical variables.

Differences in primary outcome measures between the intervention and the usual care group will be compared using independent-samples T-tests or Mann-Whitney U-tests, as appropriate. The Wilcoxon Signed Rank Test will be used to compare changes in primary outcome measures within the intervention and usual care group. Multivariate regression models will be developed to compare changes in primary and secondary outcome measures between the intervention and control group while clustering by physician and controlling for possible confounders. Finally, concordance between the patient's preferences for end-of-life care and the end-of-life care received will be calculated using Intraclass Correlation Coefficients (ICC) for continuous variables and Cohen's kappa for categorical variables.

All statistical analyses will be performed using statistics software (SPSS version 21.0 for Windows, Chicago, IL, USA) and STATA 11.1 (StataCorp LP, College Station, TX, USA) for clustered regression analysis. A priori, a two-tailed *p*-value of <0.05 was considered as significant.

**Ethics and dissemination**

The protocol of the present study has been approved by the Medical Ethical Committee of the Catharina Hospital Eindhoven, the Netherlands (NL42437.060.12) and is registered in the Dutch Trial Register (NTR3940). The study will be monitored according to the guidelines of the Dutch Federation of University Medical Centres (NFU) and will be conducted in accordance with the Medical Research Involving Human Subjects Act (WMO). The results will be submitted for publication in peer-reviewed journals and will be presented at (inter)national conferences. Participants will be informed about the results of the study. The results of this project provide direction for further development of palliative care for patients with COPD.

**DISCUSSION**

The present study has been designed to examine whether and to what extent structured ACP by a trained nurse, in collaboration with the chest physician, can improve outcomes for patients with advanced COPD and their family. The study has several strengths and limitations which will be described below.

**Strengths**

The current project is designed to improve ACP by overcoming the previously reported physician-endorsed barriers towards ACP. The most common barrier to communication about end-of-life care, endorsed by physicians, is lack of time[12]. The present study will overcome this barrier, because the intervention will be delivered by trained respiratory nurses. Nurses have specific communication skills important for end-of-life care communication, like listening to patients, being responsive to emotional needs, treating the whole person and respecting patients' cultural and religious beliefs[21]. Another barrier frequently endorsed by physicians is their assumption that patients are not ready to talk about end-of-life care[12]. However, research has shown that patients with severe to very severe

COPD have clear preferences concerning life-sustaining treatments and are willing to discuss end-of-life care[11 22]. These discussions about end-of-life care are particularly important for patients with COPD, because they follow a disease trajectory characterized by a gradual decline in health status and punctuated by exacerbations[23]. Although survival in patients with COPD is hard to predict[24], research has shown that exacerbations are associated with an increased risk of dying[25]. Patients who survived a hospitalization for an exacerbation often experience an increase in the intensity of dyspnea and had a poor quality of life[26 27]. Therefore, clinicians see exacerbations as a clinical event that defines an important transition in the course of the disease and is therefore a moment to initiate ACP[28]. In addition, patients who were hospitalized for an exacerbation describe the hospital admission itself as chaotic, but are willing to discuss their preferences for end-of-life care after discharge[29]. Consequently, an approach may be to discuss ACP after discharge.

The present study also has some methodological strengths. *First*, the present study is a randomized controlled trial. This study design in general has good validity and causal conclusions can be drawn[30]. *Second*, patients will be recruited in one academic and two general hospitals in the Netherlands to guarantee internal and external validity. *Finally*, we will perform cluster-analysis to prevent cross-contamination between the intervention and usual care group and allocation is concealed using sealed opaque envelops in order to prevent systematic biases.

**Limitations**

The present study has the following limitations:

*First*, it may be possible that eligible patients and family members who refuse participation in this study are less willing to discuss issues concerning end-of-life care than participating patients and family members. Demographics will be collected from eligible patients and family members who refuse participation in the study for comparison with participating patients and family members. However, since these patients may also refuse an ACP intervention in clinical practice, this may mitigate the importance of this limitation. *Second*, drop-out is to be expected and unavoidable in a

longitudinal study including patients with severe disease. We expect about 23% of the patients to die during the study period[31]. In addition, we expect about 10% to withdraw because of other reasons[22]. *Third*, in the present study the perception of the patient of communication about end-of-life care will be assessed. The present project does not provide objective measures for quality of communication. In addition, the present project assesses the family members' perception of quality of end-of-life care and quality of dying and does not provide objective measures for quality of end-of-life care and quality of dying. However, we believe that the perception from the patient and his or her family members is the most important construct with respect to end-of-life care. Moreover, validated instruments will be used to assess the patient perception from quality of communication about end-of-life care[15] and the family members' perception of quality of end-of-life care and quality of death and dying[17 18]. *Fourth*, quality of end-of-life care and quality of dying will be assessed retrospectively. We do not assess prospectively quality of end-of-life care in terminally ill patients. Prospectively identifying terminally ill patients with COPD is extremely difficult[10]. Moreover, we want to avoid extra burden for dying patients. However, retrospective assessments may be altered by grief or recall difficulties[32]. This should be taken into account in interpreting the results. *Fifth*, it may be possible that quality of communication about end-of-life care at baseline is different between the physicians in the intervention group and physicians in the usual care group. Therefore, data-analysis will correct for baseline QOC scores. *Sixth*, it may be possible that participants in the usual care group will be stimulated to discuss their life-sustaining treatment preferences or end-of-life care due to the assessment of their preferences during the study period. However, a prior study suggested that these questionnaires do not have a significant effect on discussions about end-of-life care[33]. *Finally*, the current intervention consists of a single session with a trained respiratory nurse specialist and providing a feedback form. We acknowledge that ACP should not be a single intervention, but should be an on-going process between patients, their loved ones and professional caregivers during the course of the disease. However, the aim of the intervention in the present study is to facilitate the on-going process of ACP between patients, families and physicians.

**Clinical consequences**

The present study will examine the effects of structured ACP by a trained respiratory nurse. When this relatively simple intervention is able to improve outcomes for patients regarding end-of-life care and their loved ones, the project can be followed by implementation of ACP in regular clinical care. In addition, the current project provides recommendations for guidelines on palliative care in COPD. Moreover, if the current intervention is able to improve outcomes for patients with COPD and their families, this program can possibly be implemented for other patients with advanced chronic life-limiting diseases, like congestive heart failure or idiopathic pulmonary fibrosis. Indeed, mortality rates are also high in these patient populations[34 35].

**Conclusion**

To date, ACP for patients with severe to very severe COPD is uncommon and poorly done. The present study aims to improve quality of end-of-life care communication, as well as quality of end-of-life care and quality of dying for patients with COPD using structured ACP by a trained nurse, in collaboration with the patient's chest physician. This study is necessary to develop an evidence based ACP program in the Netherlands. Here, the study protocol is described and a preliminary analysis of the possible strengths and weaknesses is outlined.

**Acknowledgements**

*Contributors*

EFMW is the principal investigator and together with DJAJ and MAS designed and established the study. CHMH is responsible for recruitment, data collection, and data analysis. All authors have read and approved the final version of the manuscript.

*Competing interests*

The authors have no conflicts of interest that are directly relevant to the content of this article.

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*Ethics approval*

Ethics approval has been obtained from the Medical Ethical Committee of the Catharina Hospital Eindhoven, The Netherlands (NL42437.060.12).

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## TABLES

**Table 1 Elements of structured ACP intervention**

| |
|---|
| Reflection upon patient's goals, values, and beliefs |
| Understanding the current and future medical situation, possible treatments and outcomes |
| Understanding life-sustaining treatments |

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|---|
| Determining wishes regarding current and future care |
| Encouraging discussions of ACP with health care providers and loved ones |
| Appointment of a surrogate decision maker |

**FIGURES**

**Figure legends**

Figure 1: Timing of the interviews and intervention: all patients receive data collection in the blue boxes; only patients of clinicians randomized to the intervention group receive the intervention.

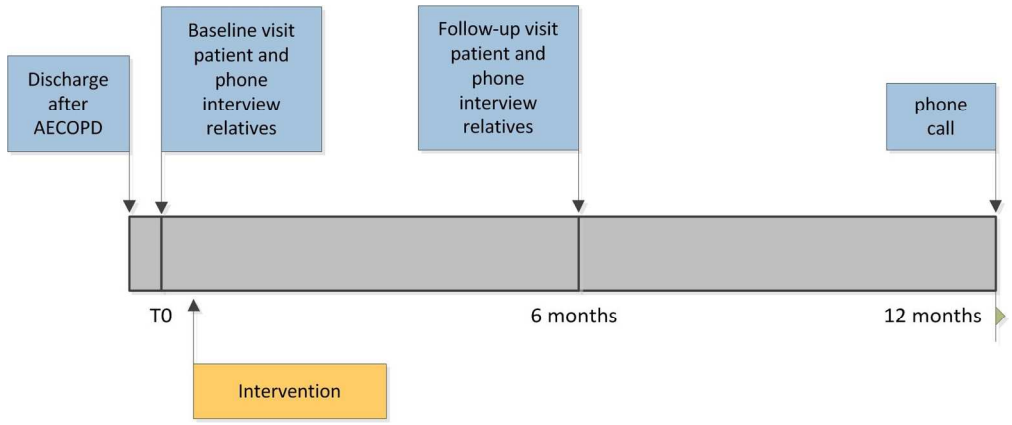


Figure 1: Timing of the interviews and intervention: all patients receive data collection in the blue boxes; only patients of clinicians randomized to the intervention group receive the intervention.
156x65mm (300 x 300 DPI)


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 | 2 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | _____ |
| Protocol version | 3 | Date and version identifier | _____ |
| Funding | 4 | Sources and types of financial, material, and other support | 14 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1, 14 |
| | 5b | Name and contact information for the trial sponsor | 14 |
| | 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 | 14 |
| | 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) | n.a. |

| | | | |
|---|---|---|---|
| **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 | 4 |
| | 6b | Explanation for choice of comparators | _____ |
| Objectives | 7 | Specific objectives or hypotheses | 5 |
| 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) | 5 |
| **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 | 5 |
| 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) | 5-6 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 6 |
| | 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) | _____ |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | _____ |
| 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 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 5, 19 |

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|---|---|---|---|
| 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 | 8 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 8 |
| **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 | 8 |
| 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 | 8 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 8-9 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | n.a. |
| | 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 | 7-8 |
| | 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 | _____ |

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| 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 | 9 |
| 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 | 10 |
| | 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 | _____ |
| 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 | _____ |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | _____ |
| **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) | _____ |

| | | | |
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| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 8 |
| | 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 | 14 |
| 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 | 10 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | _____ |
| | 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 | 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.