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Advance care planning in incurable cancer patients: a randomised controlled trial. The study protocol

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ABSTRACT

Introduction: There is limited evidence documenting the effectiveness of Advance Care Planning (ACP) in cancer care. The present randomised trial is designed to evaluate whether the administration of formal advance care planning improves compliance with patients' end-of-life wishes and patient and family satisfaction with care.

Methods and analysis: A multi-centre randomised control trial in 8 oncology centres across New South Wales and Victoria, Australia designed to assess the efficacy of a formal advance care planning intervention for cancer patients. Patients with incurable cancer and an expected survival of 3-12months, plus a nominated family member or friend will be randomised to receive either standard care or standard care plus a formal ACP intervention. The project sample size is 210 patient /nominated family or friend dyads. The primary outcome measure is family/friend reported: a) discussion with the patient about their EOL wishes and b) perception that the patient's EOL wishes were met. Secondary outcome measures include: the documentation of and compliance with patient preferences for medical intervention at the end of life; the family/friend's perception of the quality of the patient's death; the impact of death on surviving family; patient/family and patient/healthcare provider communication about end of life care; patient and family/friend satisfaction with care; quality of life of patient and family/friend subsequent to trial entry, the patient's strength of preferences for quality of life and length of future life; the costs of care subsequent to trial entry, and place of death.

Ethics and dissemination Ethical approval was received from the Sydney Local Health District (RPA Zone) Human Research Ethical Committee, Australia (Protocol number X13-0064).

Trial Registration: Australia and New Zealand Clinical Trials Registry ACTRN12613001288718

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INTRODUCTION

Despite the putative benefits of Advance Care Planning (ACP) and international initiatives aimed at improving end of life care[1], research in this field is limited. In a recent review of 113 studies on the effects of advance care planning, 95% were observational studies, 81% originated from the United States and only 18% reported on complex ACP interventions [2]. Only two studies reporting on complex interventions included patients with cancer [3 4]. The effects of ACP in cancer patients are unknown. The present trial is designed to evaluate whether the administration of a coordinated advance care planning intervention improves compliance with patient's end of life wishes, patient and family satisfaction with care and the experience of death and dying.

OBJECTIVE

The objective of the ACP study is to evaluate the efficacy of a formal advance care planning (ACP) intervention for patients with incurable cancer who have received systemic therapy (chemotherapy, targeted therapy or endocrine therapy) and have an estimated survival of 3 to 12 months.

We hypothesise that patients randomised to intervention will be more likely to have their End of Life (EOL) wishes documented and complied with. For secondary outcomes we hypothesise that patients participating in the intervention will have an improved quality of death, have nominated family or friends who experience less mental ill health during bereavement, report improved quality of communication about EOL care, report greater satisfaction with care and value quality over quantity of life more than patients in the control arm.

We hypothesise that advance care plans will reduce health care costs at the EOL; oncologists predictions of expected survival time will be inaccurate; communication of expected survival time in terms of typical, best-case and worse-case scenarios will increase patient understanding of their prognosis; and that patients and nominated family/friends will report satisfaction with the intervention.

METHODS AND ANALYSIS

Study design

The ACP trial is a prospective multi-site randomised control trial with two parallel groups receiving either usual care plus a coordinated ACP intervention or usual care without coordinated ACP. Participants enter the trial as dyads: a person diagnosed with cancer plus a nominated family member or friend. After recruitment the patient and/or family will be contacted by telephone at 8 week and then 3 month intervals until the patient's death. Family members or friends will be contacted 3 months after bereavement to complete final questionnaires. Following the patient's death, a review of their medical record will assess documentation of EOL preferences and medical interventions received in the final 2 weeks of life.

The primary outcome measure is family or friend reported: a) discussion with the patient about their EOL wishes and b) perception that the patient's EOL wishes were met.

The trial is sponsored by a National Health and Medical Research Council Project Grant APP1050596.

The study is planned for a 3 year duration with a maximum 12 month follow up period for patients and a maximum 15 month follow up period for nominated family members or friends. The study is registered on the Australia and New Zealand Clinical Trials Registry ACTRN12613001288718.

Participants

To be eligible for the ACP study patients must be 18 years or older, have a diagnosis of incurable cancer, have received systematic therapy to treat their cancer, and have an expected survival time of 3 -12 months. They must also be able to nominate a family member or friend who is willing to participate in the trial with them. All participants must be able to read and write English, and be capable of reading an information booklet and completing a series of questionnaires. Patients are excluded from the trial if they have previously completed formal advance care planning.

A total of seven oncology departments across two Australian states are actively recruiting to the trial: 2 oncology units in Melbourne (Austin & Box Hill Hospitals) and 5 in Sydney (The Chris O'Brien Life house, Campbelltown Hospital, Concord Repatriation General Hospital, The Royal North Shore Hospital and the Northern Cancer Institute).

Intervention

Participants in the trial randomised to the intervention receive formal advance care planning. Experienced oncology nurses or allied health professionals participate in a two part training course and peer mentoring and shadowing in the clinical environment, to learn to deliver the study intervention. The intervention is based on the Respecting Patient Choices model (http://www.respectingpatientchoices.org.au/) with the addition of skills in EOL communication and estimating and communicating typical, best-case and worst-case scenarios for survival. Patients in the intervention group will be offered optional information about their likely life expectancy as part of the ACP intervention. ACP clinicians participate in 8 hours of online training, 3 days of face to face workshops and two days of shadowing and peer mentoring in the clinical environment, to learn to deliver the intervention. The intervention is specifically targeted to advanced cancer patients with input from the investigator team, including oncologists and palliative care physicians. Core components of the intervention are outlined in Figure 1.

The ACP meeting occurs within 2 weeks of enrolment into the study and includes the patient and their nominated family or friend. Patients are instructed that should their goals and wishes change at any stage, they should contact their ACP nurse to arrange another meeting. All ACP meetings are audiotaped for quality and training purposes. Meetings will be audited to assess adherence and quality.

Data collection and follow up

Patients are assessed at baseline, 8 weeks (6 weeks post intervention), then every 3 months until death or the end of the study. Nominated family or friends are assessed at Baseline, 8 weeks, every 3 months until the patient's death and at 3 months after the patient's death. Figure 2 shows a schema of work flow throughout the study. The assessment schedule for patients and family/friends are summarised in Table 1 and Table 2. Following the patient's death, a review of their medical record will assess documentation of EOL preferences and medical interventions received in the final 2 weeks of life.

Table 1: Patient assessment schedule

Outcome	Measurement tool	Validated	Baseline	8weeks	Every 3months	After death
Demographics	Demographic questionnaire		✓			
Patient understanding of survival time	Prognosis survey and the itool	✓	✓	✓		
Patient/family/ healthcare provider communication about end of life care	EOL communication with family and healthcare providers questionnaire		✓	✓		
Quality of life	EQ-5D5L	✓	✓	✓	✓	
Preference for quantity or quality of life	Discrete choice experiment		✓	✓		
Patient satisfaction with care	Satisfaction with care survey		✓	✓		
Costs of ACP	Costs of care survey		✓	✓	✓	
Satisfaction with intervention	Satisfaction with ACP intervention (intervention arm only)			✓		
The documentation of patient preferences for EOL care and concordance with care received at the end of life	Medical record review form					✓
Prevalence, timing and location of EOL care documents	Medical record review form					✓

Table 2: Family/friend assessment schedule

Domain	Measurement tool	Validated	Baseline	8weeks	Every 3months	3 months after bereavement
Demographics	Demographic questionnaire		✓			
Quality of life	SF-12	✓	✓	✓	✓	✓
Bereavement adjustment	HADS	✓	✓	✓	✓	✓
The impact of death on surviving family members	Impact of event scale	✓				✓
Quality of end of life care	Quality of end of life and satisfaction with care questionnaire					✓

Study data will be collected and managed using REDCap electronic data capture tools hosted at The University of Sydney. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies.

Primary outcome

There are no validated or 'gold standard' procedures for measurement of compliance between patient's EOL wishes and the care provided [5]. To determine the extent to which the patient's end of life wishes were met we will use family perception that the patients EOL wishes were met and medical record review.

For the primary outcome of this study we will assess: family or friend reported: a) discussion with the patient about their EOL wishes and b) perception that the patient's EOL wishes were met, assessed at 3 months after bereavement. Specifically, family/friends will be asked:

- "Did the patient discuss with you any particular wishes he/she had about the care they would want to receive if they were dying". Answers will be recorded on a five point likert scale from 0 = "Not at all" to 5 = "Very much".
- "I am satisfied that at the end of his/her life their wishes were met". Answers will be recorded on a five point likert scale from 0 "Strongly disagree" to 5 = "Strongly agree".

Agreement that EOL wishes were discussed (responses of "Quite a bit" and "Very much") AND that the patients end of life wishes were met (responses of "Agree" or "Strongly agree") will be scored as a positive outcome (i.e. wishes known and complied with).

Secondary outcomes

(C) The documentation of patient preferences for EOL care and concordance with care received at the end of life;

Medical record review will assess concordance between documentation of preferences for care defined in the literature as important EOL care goals [4 6 7], and medical interventions received in the last 2 weeks of life. We will identify documented patient preferences for place of death, cardiopulmonary resuscitation, Intensive Care admission and any other significant intervention identified in a patient's medical record, including chemotherapy use within the last 4 weeks of life. Documented preferences will be compared to the care received in the last 2 weeks of life. Both documentation of preferences and concordance between preferences and care received are required to receive a positive score. Items will be scored individually.

(D) Prevalence, timing and location of EOL care documents;

Medical record review will assess the prevalence, timing and location of EOL care documents, as well as the documentation of substitute decision makers, at the hospital where patients received their oncology care.

(E) Place of death will be verified with the caregiver at the 3 month bereavement interview by asking the nominated family or friends "Where did your loved one die?"

(E) Quality of end of life care will be measured using a study specific 27 item tool assessing the family/friend's satisfaction with the quality of a patient's death. Assessment will be completed via an interview with the family/friend at 3 months after bereavement and includes items adapted from Detering et al [8] and Endelberg et al. Quality about End of Life Communication (QOC) [9]. For example family/friends will be asked, "In your opinion, how would you rate the overall quality of the patient's death/last week of life?" And "how satisfied were you with the way in which the patient died?"

(F)The impact of death on surviving family members will be measured using the impact of events scale (IES) [10] at 3 months after bereavement. This is a validated 15 item tool that identifies risk of developing post traumatic stress disorder. In addition the well validated and widely used 14 item hospital anxiety and depression scale (HADS)[11] will be measured at baseline, every 3 months until the patient's death and 3 months after bereavement .

(G) Patient/family and Patient/healthcare provider communication about end of life care will be assessed using items adapted from Wright et al [4].

(H)Patient and caregiver satisfaction with care will be assessed using a 5 question survey utilised in a previous trial [8] focusing on satisfaction with information provision.

(I) Quality of life (QOL) will be measured utilising the EQ-5D5L [12] for patients and the SF12 [13] for caregivers. QOL scores will be compared between groups and in the same group at different time intervals. Multivariate relationships between patients' quality of life and different outcomes of the intervention will also be examined.

(J) Patients' strength of preferences for quality of life and length of future life will be assessed using a Discrete Choice Experiment (DCE)[14]. Patients are presented with a

short description of a health state then asked to compare 2 descriptions and select which represents the better or more desired situation.

(K) The cost of advance care planning and the costs of health care used (for 3 months prior to trial entry until death) will be assessed. Costs of care will be assessed by data linkage using Commonwealth Medicare and PBS records, state based records on hospital admissions and emergency department visits, as well as patient reported out of pocket expenses and health care use of services and products that are beyond the scope of the administrative datasets. To determine the wider ramifications of the intervention, health care use cost of the nominated family member or friend will also be obtained both before and after the patient's death.

(L)Accuracy of predictions of life expectancy will be assessed by comparing the oncologist's estimate of each patient's life expectancy at baseline with the patient's observed survival time using methods developed in a previous study[15].

(M)Patient understanding of life expectancy will be assessed at baseline and at 8 weeks using an instrument developed in a previous study [16 17]. Patients in the intervention group who want information on life expectancy will be provided with individualised estimates of worst-case, typical and best-case scenarios for survival using the oncologist's estimate and, a web-based tool (iTool) developed by Kiely et al[17].

(N)Patient and family satisfaction with the ACP intervention will be assessed using a study developed questionnaire.

Sample size

In a previous trial by the investigator group EOL wishes were known and respected in 86% of the intervention group compared to 30% of controls [8]. Assuming the same baseline rate of EOL wishes known and respected in cancer patients, and believing a doubling to 60% would influence clinical practice, two study groups that each include 56 patients who die within the 3 year follow up period will result in the study having 90% power to detect a between-group difference with 95% certainty. A conservative estimate of mortality is 75%. To allow for incomplete data on 20% of patients and a further 10% of their nominated family members or friends, we propose a sample size of 210 patients with advanced incurable cancer.

Recruitment and Randomisation

Oncologists at participating sites will be asked to identify patients who meet the study inclusion criteria and to inform patients about the study during their outpatient oncology visits. Potential participants will be introduced to a research team member in attendance at the clinic who will provide them with further details of the study. Family members or friends who are not in attendance at the clinic will receive a follow up phone call from the research team.

Participants will be randomised by minimisation with a 1:1 allocation of control group to intervention group. Participants will be stratified by site and gender, using the 24/7

IVRS (Interactive Voice Response System) telephone based randomisation system at the National Health and Medical Research Council (NHMRC) Clinical Trials Centre.

The statistical analysis and preparation of tables and graphs for the report of the study by the statistician of the study will be blinded. Research staff completing follow up assessment and medical record review will be blinded to the extent possible (participants will be identifiable by study ID only, but the 8 week assessment contains additional 'satisfaction with the intervention' questionnaire for intervention participants and the medical record may include study specific documents). Participants and oncologists will be non-blinded.

Statistical analysis

The study statistician performing the analysis will be blinded to group allocation. The effect of the ACP intervention will be assessed by using chi-squared tests for categorical outcomes and t-tests for continuous outcomes, if measured at one time point only and if there is no oncologist effect. Clustering by oncologist will be tested using mixed models, and if the intra-cluster correlation is estimated to be non-zero, outcomes will be analysed using mixed models and generalised linear mixed models with oncologist included as a random effect. Outcomes which are measured repeatedly (e.g. QoL, satisfaction with care) will be analysed with mixed models, to assess patterns over time as well as differences between group at specific time points. These models are valid for data that are missing completely and missing at random [18] . All analyses will follow the intention to treat. Mixed models are consistent with an intention to treat analysis in the presence of missing data [19] . A secondary per-protocol analysis will be performed along with an exploration of why any participants did not receive the treatment to which they were assigned. Accuracy of predictions of survival time will be investigated using descriptive statistics and Bland-Altman plots [20]. Differences in survival will be explored with Kaplan Meier plots.

Descriptive statistics will be used to describe the sample and to compare the characteristics of patients in the different groups.

Interim analyses plan

Analysis of satisfaction with intervention and QOL data will be undertaken at mid-point of the study to ensure no adverse consequences.

DISCUSSION

The study has several strengths and limitations which are described below.

Strengths

The study design follows that of a previous randomised controlled trial conducted by members of the investigator team [8]. Therefore both the study protocol and intervention have been proven to be feasible and successful in a different patient population. Furthermore, the ACP intervention used in the present study has a number of specific strengths. Firstly, it includes both patients and their family member or friend. Secondly,

the ACP intervention is available to participants assigned to intervention for as many sessions as they request. Thirdly the ACP intervention has been adapted to be cancer specific and lastly the intervention includes optional provision of and discussion of prognostic information. The study also has methodological strengths. The ACP study is a randomised controlled trial with allocation concealed using a computer generated interactive voice system in order to prevent systematic bias.

Limitations

The proportion of eligible patients who participate in the trial will be documented. It is likely that there will be systematic differences between those who choose to participate in the ACP trial and those who choose not to participate. Secondly, it is likely that completing study questionnaires will prompt some participants in both arms of the study to consider and discuss their end of life wishes. Thirdly, it is unavoidable that in conducting a longitudinal study involving patients with incurable disease a number of participants will die before follow up data can be collected, withdraw from the study or be lost to follow up. Lastly, as the ACP intervention requires the involvement of treating oncologists and documentation in the medical record both the oncologists and researchers working in the study cannot be blinded to group allocation.

Two other RCT's are underway, which also investigate the effects of ACP in cancer [21 22] . This presents an opportunity for meta-analysis of data on the effectiveness of ACP in cancer care. Data will be collected for almost 2000 advanced cancer patients across Europe, The USA and Australia. Shared patient outcomes across all three studies include: concordance with EOL wishes and care received, quality of communication, quality of death, patient mental health outcomes and acceptability of the ACP intervention. However, there are no gold standard outcomes, or measures to assess the efficacy of ACP, and a variety of measures will be used across studies to assess similar outcomes. This presents a challenge to meta-analysis. Table 3 presents details of study design, sample size, population, intervention and primary outcome measure for each study. Shared patient outcomes and a brief description of the distinguishing features between studies are also presented. A full list of the outcome measures used in each study can be found in the published study protocols[21 22]

Table 3: Details and comparison between three RCT's of ACP in cancer care

Study name	Study design	Sample size	Population	Intervention	Primary outcome	Shared patient outcomes	Distinguishing features of each study*
ACTION Study[22]	Cluster RCT	1334	Patients with advanced lung or colorectal cancer	Adapted Respecting Patient Choices model	Quality of Life	Goal concordant care Quality of life Quality of death Satisfaction with the intervention Timing, place and prevalence of documentation about EOLC Place of death Resource use/cost analysis	Shared decision making/Patient involvement/Coping with illness Qualitative study of patients, relative and professional caregivers experiences of involvement in ACP
Bernacki[21]	Cluster RCT	426	Patients with advanced incurable cancer and a life expectancy of less than 12 months	A multi-component, structured communication intervention	Receipt of goal-concordant care, and peacefulness at the EOL		Clinician outcome data – attitudes, confidence, acceptability, prognostic evaluation
Australian ACP study	One to one randomisation RCT	210	Patients with advanced cancer, and a life expectancy of 3-12 months	Adapted Respecting Patient Choices model + prognostic information	Family or friend reported: a) discussion with the patient about their EOL wishes and b) perception that the patient's EOL wishes were met		Estimating and discussing survival scenarios Bereavement outcomes for family/friends

ETHICS AND DISSEMINATION

The study will be conducted in accordance with the National Health and Medical Research Council's guidelines for the ethical conduct of human research. The results will be submitted for publication in peer-reviewed journals and will be presented at national and international conferences. The results of this study will provide evidence for the direction and development of quality EOL care for patients with advanced cancer.

ABBREVIATIONS

ACP Advance care planning

EOL End of life

QOL Quality of Life

COMPETING INTERESTS

The author(s) declare that they have no competing interests

AUTHOR'S CONTRIBUTIONS

Stephanie Johnson is the study coordinator and drafted the manuscript. All authors contributed to the study design and review of the manuscript.

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Figure 1: Core components of the ACP intervention

I.	Negotiate an agenda for the consultation
II.	Assess the patient's and/or family's readiness to discuss future care
III.	Explore the patients understanding of their medical situation, any unmet information needs and provide information if appropriate,
IV.	Explore the patient's values, goals, priorities, hopes, fears and concerns for the future,
V.	Explore if there are any situations, treatments or health states the patient would find unacceptable
VI.	Summarise your understanding of the person's most important wishes for future care
VII.	Consider any other specific treatment options relevant to the person's circumstances
VIII.	Consider offering to make a recommendation for future medical care, if they were to become too sick to speak for themselves, based on their values and wishes,
IX.	Help the patient to document their wishes

Figure 1: Core components of the ACP intervention

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Figure 2: Participant assessment and follow up plan

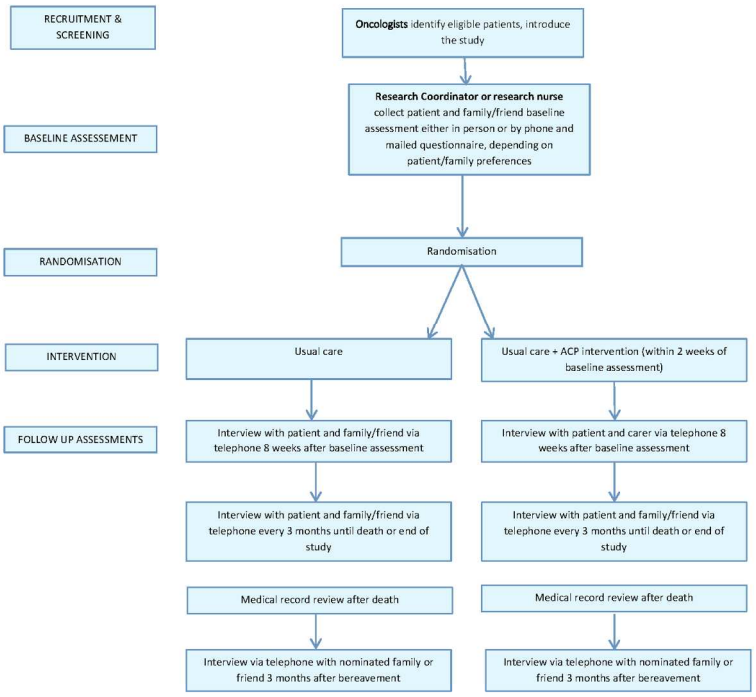

Figure 2: Participant assessment and follow up plan

210x297mm (200 x 200 DPI)

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	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
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	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
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
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)

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
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)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	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
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)
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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

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

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 enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	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
	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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	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)
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

	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
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)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	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
	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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"Advance care planning in incurable cancer patients: study protocol for a randomised controlled trial."

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Keywords:	Advance care planning, Advance Directive, End of Life, Randomised controlled trial

"Advance care planning in incurable cancer patients: study protocol for a randomised controlled trial."

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ABSTRACT

Introduction: There is limited evidence documenting the effectiveness of Advance Care Planning (ACP) in cancer care. The present randomised trial is designed to evaluate whether the administration of formal advance care planning improves compliance with patients' end-of-life wishes and patient and family satisfaction with care.

Methods and analysis: A multi-centre randomised control trial in 8 oncology centres across New South Wales and Victoria, Australia designed to assess the efficacy of a formal advance care planning intervention for cancer patients. Patients with incurable cancer and an expected survival of 3-12months, plus a nominated family member or friend will be randomised to receive either standard care or standard care plus a formal ACP intervention. The project sample size is 210 patient /nominated family or friend dyads. The primary outcome measure is family/friend reported: a) discussion with the patient about their EOL wishes and b) perception that the patient's EOL wishes were met. Secondary outcome measures include: the documentation of and compliance with patient preferences for medical intervention at the end of life; the family/friend's perception of the quality of the patient's end of life care; the impact of death on surviving family; patient/family and patient/healthcare provider communication about end of life care; patient and family/friend satisfaction with care; quality of life of patient and family/friend subsequent to trial entry, the patient's strength of preferences for quality of life and length of future life; the costs of care subsequent to trial entry, and place of death.

Ethics and dissemination Ethical approval was received from the Sydney Local Health District (RPA Zone) Human Research Ethical Committee, Australia (Protocol number X13-0064).

Trial Registration: Australia and New Zealand Clinical Trials Registry ACTRN12613001288718

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INTRODUCTION

End-of-life care is a key component of essential services for people with advanced cancer[1 1]. Unfortunately, End of Life (EOL) care of cancer patients has not kept pace with improvements in treatments directed at the cancer. Whilst evidence shows that most patients with cancer prefer to die at home or in a hospice, hospital remains the most common place of death[2 3]. In a recent study, 65% of 28,000 patients with advanced solid tumors were found to have received at least 1 form of aggressive care within the last 30 days of life[4]. Aggressive care in this study was defined as either hospital admission, an intensive care unit (ICU) admission, or an emergency room visit, as well as a chemotherapy or radiation treatment. Apart from the psycho-emotional trauma, such late interventions have significant costs both for the health system and the patient and their family.

Advance Care Planning (ACP) refers to the process by which patients, families and health professionals discuss and establish future goals of care in accordance with a patient's values and preferences. ACP is intended to support patients in receiving the care they would have chosen should they become too unwell to make their own EOL decisions near death. There is some evidence that complex ACP interventions may increase the frequency of out-of-hospital and out-of-ICU care and increase compliance with patients' end-of-life wishes [5]. However, the frequency of EOL discussions in cancer care is low [6] and limited research has been undertaken on the impact of complex ACP interventions in cancer. In a 2014 review of 113 studies on the effects of advance care planning only 18% (twenty studies) reported on complex ACP interventions and only two of these studies included patients with cancer [5]. Although ACP has the potential to improve the quality of death for patients with cancer, the effects of complex ACP interventions in the cancer population are unknown. The present trial is designed to evaluate whether the administration of a coordinated advance care planning intervention improves compliance with patient's end of life wishes, patient and family satisfaction with care and the experience of death and dying.

OBJECTIVE

The objective of the ACP study is to evaluate the efficacy of a formal advance care planning (ACP) intervention for patients with incurable cancer who have received systemic therapy (chemotherapy, targeted therapy or endocrine therapy) and have an estimated survival of 3 to 12 months.

We hypothesise that patients randomised to intervention will be more likely to have family/friend report: a) discussion with the patient about their EOL wishes and b) perception that the patient's EOL wishes were met. For secondary outcomes we hypothesise that patients participating in the intervention will be more likely to have their end of life preferences documented and complied with, have an improved quality of end of life care , have nominated family or friends who experience less mental ill health during bereavement, report improved quality of communication about EOL care, report greater satisfaction with care and value quality over quantity of life more than patients in the control arm.

We hypothesise that advance care plans will reduce health care costs at the EOL; oncologists predictions of expected survival time will be inaccurate; communication of expected survival time in terms of typical, best-case and worse-case scenarios will increase patient understanding of their prognosis; and that patients and nominated family/friends will report satisfaction with the intervention.

METHODS AND ANALYSIS

Study design

The ACP trial is a prospective multi-site randomised control trial with two parallel groups receiving either usual care plus a coordinated ACP intervention or usual care without coordinated ACP. Participants enter the trial as dyads: a person diagnosed with cancer plus a nominated family member or friend. After recruitment the patient and/or family will be contacted by telephone at 8 week and then 3 month intervals until the patient's death. Family members or friends will be contacted 3 months after bereavement to complete final questionnaires. Following the patient's death, a review of their medical record will assess documentation of EOL preferences and medical interventions received in the final 2 weeks of life.

The primary outcome measure is family or friend reported: a) discussion with the patient about their EOL wishes and b) perception that the patient's EOL wishes were met.

The trial is sponsored by a National Health and Medical Research Council Project Grant APP1050596.

The study is planned for a 3 year duration with a maximum 12 month follow up period for patients and a maximum 15 month follow up period for nominated family members or friends. The study is registered on the Australia and New Zealand Clinical Trials Registry ACTRN12613001288718.

Participants

To be eligible for the ACP study patients must be 18 years or older, have a diagnosis of incurable cancer, have received systematic therapy to treat their cancer, and have an expected survival time of 3 -12 months. They must also be able to nominate a family member or friend who is willing to participate in the trial with them. All participants must be able to read and write English, and be capable of reading an information booklet and completing a series of questionnaires. Patients are excluded from the trial if they have previously completed formal advance care planning.

A total of seven oncology departments across two Australian states are actively recruiting to the trial: 2 oncology units in Melbourne (Austin & Box Hill Hospitals) and 5 in Sydney (The Chris O'Brien Life house, Campbelltown Hospital, Concord Repatriation General Hospital, The Royal North Shore Hospital and the Northern Cancer Institute).

Intervention

Participants in the trial randomised to the intervention receive nurse led (ACP clinician) advance care planning. Patients in the intervention group will be offered optional information about their likely life expectancy as part of the ACP intervention. Experienced oncology nurses or allied health professionals participate in a two part training course and peer mentoring and shadowing in the clinical environment, to learn to deliver the study intervention. The intervention is based on the Respecting Patient Choices model[7] with the addition of skills in EOL communication and estimating and communicating typical, best-case and worst-case scenarios for survival. Treating oncologists will liaise with the ACP clinician to ensure patients understand their illness, treatment options and likely prognosis and will be asked to sign any Advance Care Plans completed by the patient. The intervention is specifically targeted to advanced cancer patients with input from the investigator team, including oncologists and palliative care physicians.

ACP clinicians complete Part 1 e-Learning Respecting Patient Choices® education course to provide a broad introduction to ACP, and Part 2 Practical workshop at Austin Hospital, Australia, based on the Respecting Patient Choices® education course [8]. ACP clinicians attend a focused one day workshop to learn additional skills in EOL communication and in delivering prognostic information. The workshop includes cancer specific clinical information and role play with professional actors. Core components of the intervention are outlined in Figure 1.

The ACP meeting occurs within 2 weeks of enrolment into the study and includes the patient and their nominated family or friend. Patients are instructed that should their goals and wishes change at any stage, they should contact their ACP nurse to arrange another meeting. All ACP meetings are audiotaped for quality and training purposes. Meetings will be audited to assess adherence and quality.

Data collection and follow up

Patients are assessed at baseline, 8 weeks (6 weeks post intervention), then every 3 months until death or the end of the study. Nominated family or friends are assessed at Baseline, 8 weeks, every 3 months until the patient's death and at 3 months after the patient's death. Figure 2 shows a schema of work flow throughout the study. The assessment schedule for patients and family/friends are summarised in Table 1 and Table 2. Following the patient's death, a review of their medical record will assess documentation of EOL preferences and medical interventions received in the final 2 weeks of life.

Table 1: Patient assessment schedule

Outcome	Measurement tool	Validated	Baseline	8weeks	Every 3months	After death
Demographics	Demographic questionnaire		✓			
Patient understanding of survival time	Prognosis survey and the itool	✓	✓	✓		
Patient/family/ healthcare provider communication about end of life care	EOL communication with family and healthcare providers questionnaire		✓	✓		
Quality of life	EQ-5D5L	✓	✓	✓	✓	
Preference for quantity or quality of life	Discrete choice experiment		✓	✓		
Patient satisfaction with care	Satisfaction with care survey		✓	✓		
Costs of ACP	Costs of care survey		✓	✓	✓	
Satisfaction with intervention	Satisfaction with ACP intervention (intervention arm only)			✓		
The documentation of patient preferences for EOL care and concordance with care received at the end of life	Medical record review form					✓
Prevalence, timing and location of EOL care documents	Medical record review form					✓

Table 2: Family/friend assessment schedule

Domain	Measurement tool	Validated	Baseline	8weeks	Every 3months	3 months after bereavement
Demographics	Demographic questionnaire		✓			
Quality of life	SF-12	✓	✓	✓	✓	✓
Bereavement adjustment	HADS	✓	✓	✓	✓	✓
The impact of death on surviving family members	Impact of event scale	✓				✓
Quality of end of life care	Quality of end of life and satisfaction with care questionnaire					✓

Study data will be collected and managed using REDCap electronic data capture tools hosted at The University of Sydney. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies[9].

Primary outcome

There are no validated or 'gold standard' procedures for measurement of compliance between patient's EOL wishes and the care provided [10]. To determine the extent to which the patient's end of life wishes were met we will use family perception that the patients EOL wishes were met.

For the primary outcome of this study we will assess: family or friend reported: a) discussion with the patient about their EOL wishes and b) perception that the patient's EOL wishes were met, assessed at 3 months after bereavement. Specifically, family/friends will be asked:

- "Did the patient discuss with you any particular wishes he/she had about the care they would want to receive if they were dying". Answers will be recorded on a five point likert scale from 0 = "Not at all" to 5 = "Very much".
- "I am satisfied that at the end of his/her life their wishes were met". Answers will be recorded on a five point likert scale from 0 "Strongly disagree" to 5 = "Strongly agree".

Agreement that EOL wishes were discussed (responses of "Quite a bit" and "Very much") AND that the patients end of life wishes were met (responses of "Agree" or "Strongly agree") will be scored as a positive outcome (i.e. wishes known and complied with).

Secondary outcomes

(A) The documentation of patient preferences for EOL care and concordance with care received at the end of life;

Medical record review will assess concordance between documentation of preferences for care defined in the literature as important EOL care goals [11-13], and medical interventions received in the last 2 weeks of life. We will identify documented patient preferences for place of death, cardiopulmonary resuscitation, Intensive Care admission and any other significant intervention identified in a patient's medical record, including chemotherapy use within the last 4 weeks of life. Documented preferences will be compared to the care received in the last 2 weeks of life. Both documentation of preferences and concordance between preferences and care received are required to receive a positive score. Items will be scored individually.

(B) Prevalence, timing and location of EOL care documents;

Medical record review will assess the prevalence, timing and location of EOL care documents, as well as the documentation of substitute decision makers, at the hospital where patients received their oncology care.

(C) Place of death will be verified with the caregiver at the 3 month bereavement interview by asking the nominated family or friends "Where did your loved one die?"

(D) Quality of end of life care will be measured using a study specific 27 item tool assessing the family/friend's satisfaction with the quality of a patient's death. Assessment will be completed via an interview with the family/friend at 3 months after bereavement and includes items adapted from Detering et al [14] and Endelberg et al. Quality about End of Life Communication (QOC) [15]. For example family/friends will be asked, "In your opinion, how would you rate the overall quality of the patient's death/last week of life?" And "how satisfied were you with the way in which the patient died?"

(E)The impact of death on surviving family members will be measured using the impact of events scale (IES) [16] at 3 months after bereavement. This is a validated 15 item tool that identifies risk of developing post-traumatic stress disorder. In addition the well validated and widely used 14 item hospital anxiety and depression scale (HADS)[17] will be measured at baseline, every 3 months until the patient's death and 3 months after bereavement .

(F) Patient/family and Patient/healthcare provider communication about end of life care will be assessed using items adapted from Wright et al [13].

(G)Patient and caregiver satisfaction with care will be assessed using a 5 question survey utilised in a previous trial [14] focusing on satisfaction with information provision.

(H) Quality of life (QOL) will be measured utilising the EQ-5D5L [18] for patients and the SF12 [19] for caregivers. QOL scores will be compared between groups and in the same group at different time intervals. Multivariate relationships between patients' quality of life and different outcomes of the intervention will also be examined.

(I) Patients' strength of preferences for quality of life and length of future life will be assessed using a Discrete Choice Experiment (DCE)[20]. Patients are presented with a short description of a health state then asked to compare 2 descriptions and select which represents the better or more desired situation.

(J) The cost of advance care planning and the costs of health care used (for 3 months prior to trial entry until death) will be assessed. Costs of care will be assessed by data linkage using Commonwealth Medicare and PBS records, state based records on hospital admissions and emergency department visits, as well as patient reported out of pocket expenses and health care use of services and products that are beyond the scope of the administrative datasets. To determine the wider ramifications of the intervention, health care use cost of the nominated family member or friend will also be obtained both before and after the patient's death.

(K)Accuracy of predictions of life expectancy will be assessed by comparing the oncologist's estimate of each patient's life expectancy at baseline with the patient's observed survival time using methods developed in a previous study[21].

(L)Patient understanding of life expectancy will be assessed at baseline and at 8 weeks using an instrument developed in a previous study [22 23]. Patients in the intervention group who want information on life expectancy will be provided with individualised estimates of worst-case, typical and best-case scenarios for survival using the oncologist's estimate and, a web-based tool (iTool) developed by Kiely et al[23].

(M)Patient and family satisfaction with the ACP intervention will be assessed using a study developed questionnaire.

Box 1 Provides further details on the medical record review data collection and assessment of intervention fidelity.

Box 1: Details of assessment of the medical record review and intervention fidelity

Medical record review for deceased patients

Trained members of the research team will consider all of a patient's available medical records (at the acute hospital where they receive their oncology care) to assess concordance between documentation of preferences for care and medical interventions received, place of death and timing and location of documentation of EOL preferences (secondary outcomes A,B and C). Reviewers will receive two days of face face to face group training, and be provided with a standard form and written guidelines. 10% of records will be re-abstracted by a second reviewer to assess for Inter-Rater Reliability. Reviewers will have real-time consultation with medically trained staff if required. Where the abstractor is unsure of how to score, cases will be referred first to the study coordinator and then to the steering committee for additional review until consensus is reached.

Intervention fidelity

All intervention sessions will be audio recorded. This provides an opportunity to assess how the intervention was actually delivered in practice. There are currently no tools available which aim to measure the quality and consistency of ACP interventions. Additionally, there have been no published reports of auditing actual practice of ACP inside of a clinical trial setting. We will use the data from the recorded ACP conversations to: (1) Design and evaluate a fidelity instrument; (2) Describe variations in ACP intervention delivery; and (3) Analyse correlations between delivery with patient outcomes.

Sample size

In a previous trial by the investigator group EOL wishes were known and respected in 86% of the intervention group compared to 30% of controls [14]. Assuming the same baseline rate of EOL wishes known and respected in cancer patients, and believing a doubling to 60% would influence clinical practice, two study groups that each include 56 patients who die within the 3 year follow up period will result in the study having 90% power to detect a between-group difference with 95% certainty. A conservative estimate of mortality is 75%. To allow for incomplete data on 20% of patients and a further 10% of their nominated family members or friends, we propose a sample size of 210 patients with advanced incurable cancer.

Recruitment and Randomisation

Oncologists at participating sites will be asked to identify patients who meet the study inclusion criteria and to inform patients about the study during their outpatient oncology visits. Potential participants will be introduced to a research team member in attendance at the clinic who will provide them with further details of the study.Family members or friends who are not in attendance at the clinic will receive a follow up phone call from the research team. The information provided in the consent form will be the same for the intervention group and the control group. The information sheets will exclude naming the intervention (Advance Care Planning) in order to avoid contamination of the control arm. Participants will be informed that the project is evaluating the effectiveness of a program aimed at improving communication with patients with advanced cancer, their family and friends and their doctors. Participants will be informed that those randomised to the intervention group will meet with a specially trained nurse to talk through their goals, wishes and needs for care now and in the future. Participants in this study will be advised before entry that participation is voluntary and they are free to withdraw at any time.

Participants will be randomised by minimisation with a 1:1 allocation of control group to intervention group. Participants will be stratified by site and gender, using the 24/7 IVRS (Interactive Voice Response System) telephone based randomisation system at the National Health and Medical Research Council (NHMRC) Clinical Trials Centre.

The statistical analysis and preparation of tables and graphs for the report of the study by the statistician of the study will be blinded. Research staff completing follow up assessment and medical record review will be blinded to the extent possible (participants will be identifiable by study ID only, but the 8 week assessment contains additional 'satisfaction with the intervention' questionnaire for intervention participants and the medical record may include study specific documents). Participants and oncologists will be non-blinded.

Statistical analysis

The study statistician performing the analysis will be blinded to group allocation. The effect of the ACP intervention will be assessed by using chi-squared tests for categorical outcomes and t-tests for continuous outcomes, if measured at one time point only and if there is no oncologist effect. Clustering by oncologist will be tested using mixed models, and if the intra-cluster correlation is estimated to be non-zero, outcomes will be analysed using mixed models and generalised linear mixed models with oncologist included as a random effect. Outcomes which are measured repeatedly (e.g. QoL, satisfaction with care) will be analysed with mixed models, to assess patterns over time as well as differences between group at specific time points. These models are valid for data that are missing completely and missing at random [24] . All analyses will follow the intention to treat. Mixed models are consistent with an intention to treat analysis in the presence of missing data [25] . A secondary per-protocol analysis will be performed along with an exploration of why any participants did not receive the treatment to which they were assigned. Accuracy of predictions of survival time will be investigated using descriptive statistics and Bland-Altman plots [26] for those patients who die within the follow up period. Differences in survival will be explored with Kaplan Meier plots.

Descriptive statistics will be used to describe the sample and to compare the characteristics of patients in the different groups.

Interim analyses plan

Analysis of satisfaction with intervention and QOL data will be undertaken at mid-point of the study to ensure no adverse consequences.

DISCUSSION

The study has several strengths and limitations which are described below.

Strengths

The study design follows that of a previous randomised controlled trial conducted by members of the investigator team [14]. Therefore both the study protocol and intervention have been proven to be feasible and successful in a different patient population. Furthermore, the ACP intervention used in the present study has a number of specific strengths. Firstly, it includes both patients and their family member or friend. Secondly, the ACP intervention is available to participants assigned to intervention for as many sessions as they request. Thirdly the ACP intervention has been adapted to be cancer specific and lastly the intervention includes optional provision of and discussion of prognostic information. The study also has methodological strengths. The ACP study is a randomised controlled trial with allocation concealed using a computer generated interactive voice system in order to prevent systematic bias.

Limitations

The proportion of eligible patients who participate in the trial will be documented. It is likely that there will be systematic differences between those who choose to participate in the ACP trial and those who choose not to participate. Secondly, it is likely that completing study questionnaires will prompt some participants in both arms of the study to consider and discuss their end of life wishes. Thirdly, it is unavoidable that in conducting a longitudinal study involving patients with incurable disease a number of participants will die before follow up data can be collected, withdraw from the study or be lost to follow up. Fourth, the study intervention is complex and requires skill, time and resources to deliver. It may be difficult to replicate consistently across institutions. Lastly, as the ACP intervention requires the involvement of treating oncologists and documentation in the medical record both the oncologists and researchers working in the study cannot be blinded to group allocation.

Two other RCT's are underway, which also investigate the effects of ACP in cancer [27 28]. This presents an opportunity for meta-analysis of data on the effectiveness of ACP in cancer care. Data will be collected for almost 2000 advanced cancer patients across Europe, The USA and Australia. Shared patient outcomes across all three studies include: concordance with EOL wishes and care received, quality of communication, quality of death/Quality of end of life care, patient mental health outcomes and acceptability of the ACP intervention. Further details of each study are presented in Table 3. However, there are no gold standard outcomes, or measures to assess the

efficacy of ACP, and a variety of measures will be used across studies to assess similar outcomes. This presents a challenge to meta-analysis. Table 3 presents details of study design, sample size, population, intervention and primary outcome measure for each study. Shared patient outcomes and a brief description of the distinguishing features between studies are also presented. A full list of the outcome measures used in each study can be found in the published study protocols[27 28]

Table 3: Details and comparison between three RCT's of ACP in cancer care

Study name	Study design	Sample size	Population	Intervention	Primary outcome	Shared patient outcomes	Distinguishing features of each study*
ACTION Study[28]	Cluster RCT	1334	Patients with advanced lung or colorectal cancer	Adapted Respecting Patient Choices model	Quality of Life	Goal concordant care Quality of life Quality of death / quality of end of life care Satisfaction with the intervention Timing, place and prevalence of documentation about EOLC Place of death Resource use/cost analysis	Shared decision making/Patient involvement/ Coping with illness Qualitative study of patients, relative and professional caregivers experiences of involvement in ACP
Bernacki[27]	Cluster RCT	426	Patients with advanced incurable cancer and a life expectancy of less than 12 months	A multi-component, structured communication intervention	Receipt of goal-concordant care, and peacefulness at the EOL		Clinician outcome data – attitudes, confidence, acceptability, prognostic evaluation
Australian ACP study	One to one randomisation RCT	210	Patients with advanced cancer, and a life expectancy of 3-12 months	Adapted Respecting Patient Choices model + prognostic information	Family or friend reported: a) discussion with the patient about their EOL wishes and b) perception that the patient's EOL wishes were met		Estimating and discussing survival scenarios Bereavement outcomes for family/friends

ETHICS AND DISSEMINATION

The study will be conducted in accordance with the National Health and Medical Research Council's guidelines for the ethical conduct of human research. The study investigator team which includes academics and clinicians with a broad range of skills and experience, has been established as a steering committee. The steering committee meet quarterly and will guide study procedures and dissemination of results." Important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) will be communicated to relevant parties via regular study newsletters. The results will be submitted for publication in peer-reviewed journals and will be presented at national and international conferences. All information collected during the course of the study will be kept strictly confidential and any information which would allow

individual participants to be identified will not be released. All participants will be assigned a study number, and confidentiality and anonymity will be maintained throughout the duration of the study and in the preparation and dissemination of results.The results of this study will provide evidence for the direction and development of quality EOL care for patients with advanced cancer.

ABBREVIATIONS

ACP Advance care planning

EOL End of life

QOL Quality of Life

COMPETING INTERESTS

The author(s) declare that they have no competing interests

AUTHOR'S CONTRIBUTIONS

Stephanie Johnson is the study coordinator and drafted the manuscript. All authors contributed to the study design and review of the manuscript.

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Figure 1: Core components of the ACP intervention

I.	Negotiate an agenda for the consultation
II.	Assess the patient's and/or family's readiness to discuss future care
III.	Explore the patients understanding of their medical situation, any unmet information needs and provide information if appropriate,
IV.	Explore the patient's values, goals, priorities, hopes, fears and concerns for the future,
V.	Explore if there are any situations, treatments or health states the patient would find unacceptable
VI.	Summarise your understanding of the person's most important wishes for future care
VII.	Consider any other specific treatment options relevant to the person's circumstances
VIII.	Consider offering to make a recommendation for future medical care, if they were to become too sick to speak for themselves, based on their values and wishes,
IX.	Help the patient to document their wishes

Figure 1: Core components of the ACP intervention

145x125mm (300 x 300 DPI)

Figure 2: Participant assessment and follow up plan

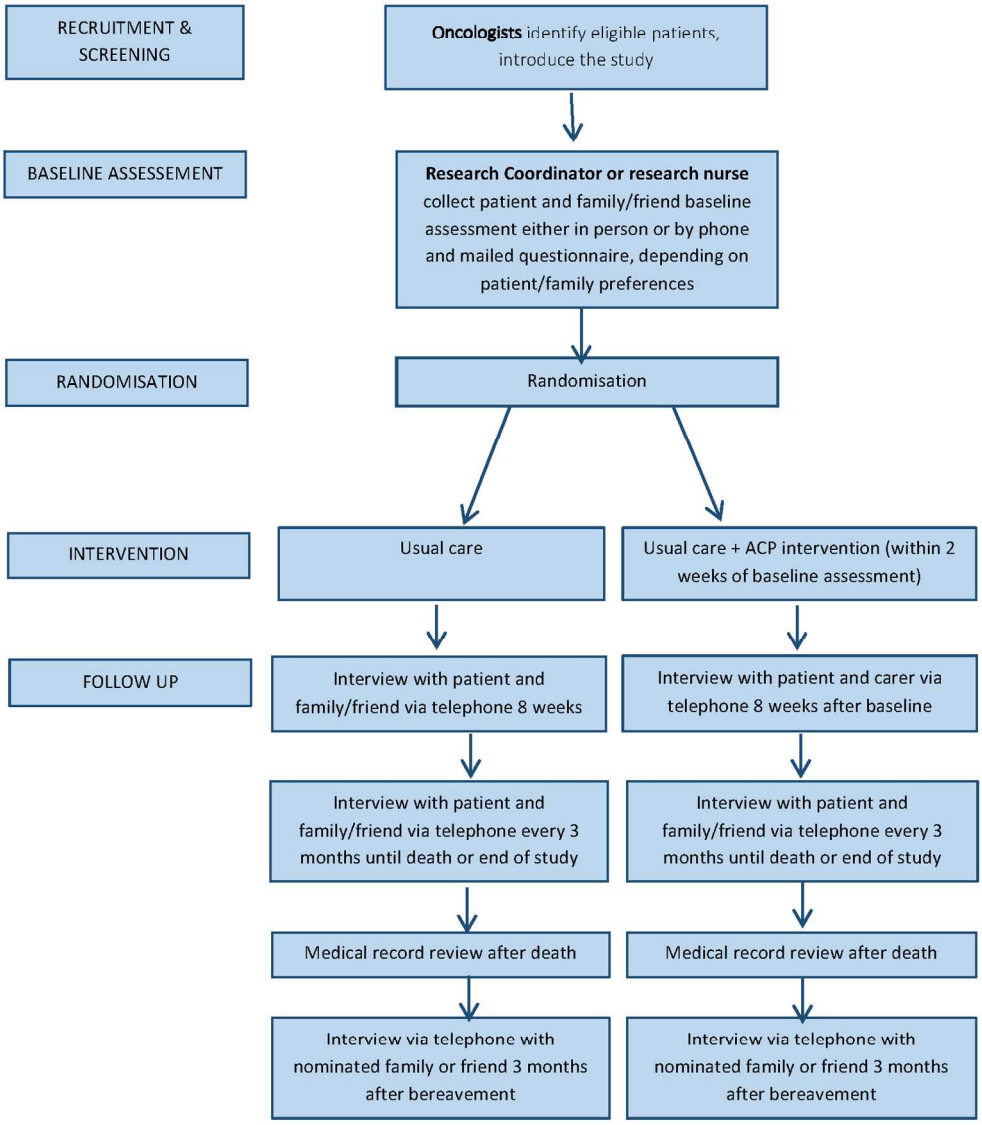

Figure 2: Participant assessment and follow up plan

143x172mm (300 x 300 DPI)

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym – Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry – Page 2
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier – title page of protocol
Funding	4	Sources and types of financial, material, and other support – Page 2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors – Page 2
	5b	Name and contact information for the trial sponsor– Page 2
	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 – Page 12
	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) – Page 12
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 – Page 3
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses – Page 3 and 4

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) – Page 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 – Page 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) – Page 4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered – Page 5
	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) – Page 5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Box 1 (page 5)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial N/A
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 – Page 7
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) – Page 6. Figure 2, Table 1 and 2
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 – Page 9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size – Page 9

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 – Page 9
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 – Page 9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions – Page 9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how– Page 9
	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 – Page 7 – 10
	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 – Page 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 – Page 5
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 – Page 10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) – Page 10
	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)

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 – Page 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 – Page 10
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 – Page 12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor – Page 12

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval – Page 12
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) – Page 12
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) – Page 9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable– NA
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– Page 12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site - NA
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 -NA
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-NA

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 – Page 12
	31b	Authorship eligibility guidelines and any intended use of professional writers NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code NA
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.

BMJ Open

"Advance care planning in incurable cancer patients: study protocol for a randomised controlled trial."

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Secondary Subject Heading:	Palliative care, Patient-centred medicine
Keywords:	Advance care planning, Advance Directive, End of Life, Randomised controlled trial

"Advance care planning in incurable cancer patients: study protocol for a randomised controlled trial."

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ABSTRACT

Introduction: There is limited evidence documenting the effectiveness of Advance Care Planning (ACP) in cancer care. The present randomised trial is designed to evaluate whether the administration of formal advance care planning improves compliance with patients' end-of-life wishes and patient and family satisfaction with care.

Methods and analysis: A randomised control trial in 8 oncology centres across New South Wales and Victoria, Australia designed to assess the efficacy of a formal ACP intervention for cancer patients. Patients with incurable cancer and an expected survival of 3-12months, plus a nominated family member or friend will be randomised to receive either standard care or standard care plus a formal ACP intervention. The project sample size is 210 patient/family or friend dyads. The primary outcome measure is family/friend reported: a) discussion with the patient about their End of Life (EOL) wishes and b) perception that the patient's EOL wishes were met. Secondary outcome measures include: documentation of and compliance with patient preferences for medical intervention at the EOL; the family/friend's perception of the quality of the patient's EOL care; the impact of death on surviving family; patient/family and patient/healthcare provider communication about EOL care; patient and family/friend satisfaction with care; quality of life of patient and family/friend subsequent to trial entry, the patient's strength of preferences for quality of life and length of life; the costs of care subsequent to trial entry, and place of death.

Ethics and dissemination: Ethical approval was received from the Sydney Local Health District (RPA Zone) Human Research Ethical Committee, Australia (Protocol number X13-0064). Study results will be submitted for publication in peer-reviewed journals and presented at national and international conferences.

Trial Registration: Australia and New Zealand Clinical Trials Registry ACTRN12613001288718

Funding: This work was supported by The National Health and Medical Research Council grant number APP 1050596

INTRODUCTION

End-of-life care is a key component of essential services for people with advanced cancer[1 1]. Unfortunately, End of Life (EOL) care of cancer patients has not kept pace with improvements in treatments directed at the cancer. Whilst evidence shows that most patients with cancer prefer to die at home or in a hospice, hospital remains the most common place of death[2 3]. In a recent study, 65% of 28,000 patients with advanced solid tumors were found to have received at least 1 form of aggressive care within the last 30 days of life[4]. Aggressive care in this study was defined as either hospital admission, an intensive care unit (ICU) admission, or an emergency room visit, as well as a chemotherapy or radiation treatment. Apart from the psycho-emotional trauma, such late interventions have significant costs both for the health system and the patient and their family.

Advance Care Planning (ACP) refers to the process by which patients, families and health professionals discuss and establish future goals of care in accordance with a patient's values and preferences. ACP is intended to support patients in receiving the care they would have chosen should they become too unwell to make their own EOL decisions near death. There is some evidence that complex ACP interventions may increase the frequency of out-of-hospital and out-of-ICU care and increase compliance with patients' end-of-life wishes [5]. However, the frequency of EOL discussions in cancer care is low [6] and limited research has been undertaken on the impact of complex ACP interventions in cancer. In a 2014 review of 113 studies on the effects of advance care planning only 18% (twenty studies) reported on complex ACP interventions and only two of these studies included patients with cancer [5]. Although ACP has the potential to improve the quality of death for patients with cancer, the effects of complex ACP interventions in the cancer population are unknown. The present trial is designed to evaluate whether the administration of a coordinated advance care planning intervention improves compliance with patient's end of life wishes, patient and family satisfaction with care and the experience of death and dying.

OBJECTIVE

The objective of the ACP study is to evaluate the efficacy of a formal advance care planning (ACP) intervention for patients with incurable cancer who have received systemic therapy (chemotherapy, targeted therapy or endocrine therapy) and have an estimated survival of 3 to 12 months.

We hypothesise that patients randomised to intervention will be more likely to have family/friend report: a) discussion with the patient about their EOL wishes and b) perception that the patient's EOL wishes were met. For secondary outcomes we hypothesise that patients participating in the intervention will be more likely to have their end of life preferences documented and complied with, have an improved quality of end of life care , have nominated family or friends who experience less mental ill health during bereavement, report improved quality of communication about EOL care, report greater satisfaction with care and value quality over quantity of life more than patients in the control arm.

We hypothesise that advance care plans will reduce health care costs at the EOL; oncologists predictions of expected survival time will be inaccurate; communication of expected survival time in terms of typical, best-case and worse-case scenarios will increase patient understanding of their prognosis; and that patients and nominated family/friends will report satisfaction with the intervention.

METHODS AND ANALYSIS

Study design

The ACP trial is a prospective multi-site randomised control trial with two parallel groups receiving either usual care plus a coordinated ACP intervention or usual care without coordinated ACP. Participants enter the trial as dyads: a person diagnosed with cancer plus a nominated family member or friend. After recruitment the patient and/or family will be contacted by telephone at 8 week and then 3 month intervals until the patient's death. Family members or friends will be contacted 3 months after bereavement to complete final questionnaires. Following the patient's death, a review of their medical record will assess documentation of EOL preferences and medical interventions received in the final 2 weeks of life.

The primary outcome measure is family or friend reported: a) discussion with the patient about their EOL wishes and b) perception that the patient's EOL wishes were met.

The trial is sponsored by a National Health and Medical Research Council Project Grant APP1050596.

The study is planned for a 3 year duration with a maximum 12 month follow up period for patients and a maximum 15 month follow up period for nominated family members or friends. The study is registered on the Australia and New Zealand Clinical Trials Registry ACTRN12613001288718.

Participants

To be eligible for the ACP study patients must be 18 years or older, have a diagnosis of incurable cancer, have received systematic therapy to treat their cancer, and have an expected survival time of 3 -12 months. They must also be able to nominate a family member or friend who is willing to participate in the trial with them. All participants must be able to read and write English, and be capable of reading an information booklet and completing a series of questionnaires. Patients are excluded from the trial if they have previously completed formal advance care planning.

A total of seven oncology departments across two Australian states are actively recruiting to the trial: 2 oncology units in Melbourne (Austin & Box Hill Hospitals) and 5 in Sydney (The Chris O'Brien Life house, Campbelltown Hospital, Concord Repatriation General Hospital, The Royal North Shore Hospital and the Northern Cancer Institute).

Intervention

Participants in the trial randomised to the intervention receive nurse led (ACP clinician) advance care planning. Patients in the intervention group will be offered optional information about their likely life expectancy as part of the ACP intervention. Experienced oncology nurses or allied health professionals participate in a two part training course and peer mentoring and shadowing in the clinical environment, to learn to deliver the study intervention. The intervention is based on the Respecting Patient Choices model[7] with the addition of skills in EOL communication and estimating and communicating typical, best-case and worst-case scenarios for survival. Treating oncologists will liaise with the ACP clinician to ensure patients understand their illness, treatment options and likely prognosis and will be asked to sign any Advance Care Plans completed by the patient. The intervention is specifically targeted to advanced cancer patients with input from the investigator team, including oncologists and palliative care physicians.

ACP clinicians complete Part 1 e-Learning Respecting Patient Choices® education course to provide a broad introduction to ACP, and Part 2 Practical workshop at Austin Hospital, Australia, based on the Respecting Patient Choices® education course [8]. ACP clinicians attend a focused one day workshop to learn additional skills in EOL communication and in delivering prognostic information. The workshop includes cancer specific clinical information and role play with professional actors. Core components of the intervention are outlined in Figure 1.

The ACP meeting occurs within 2 weeks of enrolment into the study and includes the patient and their nominated family or friend. Patients are instructed that should their goals and wishes change at any stage, they should contact their ACP nurse to arrange another meeting. All ACP meetings are audiotaped for quality and training purposes. Meetings will be audited to assess adherence and quality.

Data collection and follow up

Patients are assessed at baseline, 8 weeks (6 weeks post intervention), then every 3 months until death or the end of the study. Nominated family or friends are assessed at Baseline, 8 weeks, every 3 months until the patient's death and at 3 months after the patient's death. Figure 2 shows a schema of work flow throughout the study. The assessment schedule for patients and family/friends are summarised in Table 1 and Table 2. Following the patient's death, a review of their medical record will assess documentation of EOL preferences and medical interventions received in the final 2 weeks of life.

Table 1: Patient assessment schedule

Outcome	Measurement tool	Validated	Baseline	8weeks	Every 3months	After death
Demographics	Demographic questionnaire		✓			
Patient understanding of survival time	Prognosis survey and the itool	✓	✓	✓		
Patient/family/ healthcare provider communication about end of life care	EOL communication with family and healthcare providers questionnaire		✓	✓		
Quality of life	EQ-5D5L	✓	✓	✓	✓	
Preference for quantity or quality of life	Discrete choice experiment		✓	✓		
Patient satisfaction with care	Satisfaction with care survey		✓	✓		
Costs of ACP	Costs of care survey		✓	✓	✓	
Satisfaction with intervention	Satisfaction with ACP intervention (intervention arm only)			✓		
The documentation of patient preferences for EOL care and concordance with care received at the end of life	Medical record review form					✓
Prevalence, timing and location of EOL care documents	Medical record review form					✓

Table 2: Family/friend assessment schedule

Domain	Measurement tool	Validated	Baseline	8weeks	Every 3months	3 months after bereavement
Demographics	Demographic questionnaire		✓			
Quality of life	SF-12	✓	✓	✓	✓	✓
Bereavement adjustment	HADS	✓	✓	✓	✓	✓
The impact of death on surviving family members	Impact of event scale	✓				✓
Quality of end of life care	Quality of end of life and satisfaction with care questionnaire					✓

Study data will be collected and managed using REDCap electronic data capture tools hosted at The University of Sydney. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies[9].

Primary outcome

There are no validated or 'gold standard' procedures for measurement of compliance between patient's EOL wishes and the care provided [10]. To determine the extent to which the patient's end of life wishes were met we will use family perception that the patients EOL wishes were met.

For the primary outcome of this study we will assess: family or friend reported: a) discussion with the patient about their EOL wishes and b) perception that the patient's EOL wishes were met, assessed at 3 months after bereavement. Specifically, family/friends will be asked:

- "Did the patient discuss with you any particular wishes he/she had about the care they would want to receive if they were dying". Answers will be recorded on a five point likert scale from 0 = "Not at all" to 5 = "Very much".
- "I am satisfied that at the end of his/her life their wishes were met". Answers will be recorded on a five point likert scale from 0 "Strongly disagree" to 5 = "Strongly agree".

Agreement that EOL wishes were discussed (responses of "Quite a bit" and "Very much") AND that the patients end of life wishes were met (responses of "Agree" or "Strongly agree") will be scored as a positive outcome (i.e. wishes known and complied with).

Secondary outcomes

(A) The documentation of patient preferences for EOL care and concordance with care received at the end of life;

Medical record review will assess concordance between documentation of preferences for care defined in the literature as important EOL care goals[11-13], and medical interventions received in the last 2 weeks of life. Since published papers used varied time frames (from a few days to a month) to assess medical interventions received at the EOL, we adopted a two week time point. We will identify documented patient preferences for place of death, cardiopulmonary resuscitation, Intensive Care admission and any other significant intervention identified in a patient's medical record, including chemotherapy use within the last 4 weeks of life. Documented preferences will be compared to the care received in the last 2 weeks of life. Both documentation of preferences and concordance between preferences and care received are required to receive a positive score. Items will be scored individually.

(B) Prevalence, timing and location of EOL care documents;

Medical record review will assess the prevalence, timing and location of EOL care documents, as well as the documentation of substitute decision makers, at the hospital where patients received their oncology care.

(C) Place of death will be verified with the caregiver at the 3 month bereavement interview by asking the nominated family or friends "Where did your loved one die?"

(D) Quality of end of life care will be measured using a study specific 27 item tool assessing the family/friend's satisfaction with the quality of a patient's death. Assessment will be completed via an interview with the family/friend at 3 months after bereavement and includes items adapted from Detering et al [14] and Engelberget al. Quality about End of Life Communication (QOC) [15]. For example family/friends will be asked, "In your opinion, how would you rate the overall quality of the patient's death/last week of life?" And "how satisfied were you with the way in which the patient died?"

(E)The impact of death on surviving family members will be measured using the impact of events scale (IES) [16] at 3 months after bereavement. This is a validated 15 item tool that identifies risk of developing post-traumatic stress disorder. In addition the well validated and widely used 14 item hospital anxiety and depression scale (HADS)[17] will be measured at baseline, every 3 months until the patient's death and 3 months after bereavement .

(F) Patient/family and Patient/healthcare provider communication about end of life care will be assessed using items adapted from Wright et al [13].

(G)Patient and caregiver satisfaction with care will be assessed using a 5 question survey utilised in a previous trial [14] focusing on satisfaction with information provision.

(H) Quality of life (QOL) will be measured utilising the EQ-5D5L [18] for patients and the SF12 [19] for caregivers. QOL scores will be compared between groups and in the same group at different time intervals. Multivariate relationships between patients' quality of life and different outcomes of the intervention will also be examined.

(I) Patients' strength of preferences for quality of life and length of future life will be assessed using a Discrete Choice Experiment (DCE)[20]. Patients are presented with a short description of a health state then asked to compare 2 descriptions and select which represents the better or more desired situation.

(J) The cost of advance care planning and the costs of health care used (for 3 months prior to trial entry until death) will be assessed. Costs of care will be assessed by data linkage using Commonwealth Medicare and PBS records, state based records on hospital admissions and emergency department visits, as well as patient reported out of pocket expenses and health care use of services and products that are beyond the scope of the administrative datasets. To determine the wider ramifications of the intervention, health care use cost of the nominated family member or friend will also be obtained both before and after the patient's death.

(K)Accuracy of predictions of life expectancy will be assessed by comparing the oncologist's estimate of each patient's life expectancy at baseline with the patient's observed survival time using methods developed in a previous study[21].

(L)Patient understanding of life expectancy will be assessed at baseline and at 8 weeks using an instrument developed in a previous study [22 23]. Patients in the intervention group who want information on life expectancy will be provided with individualised estimates of worst-case, typical and best-case scenarios for survival using the oncologist's estimate and, a web-based tool (iTool) developed by Kiely et al[23].

(M)Patient and family satisfaction with the ACP intervention will be assessed using a study developed questionnaire.

Box 1 Provides further details on the medical record review data collection and assessment of intervention fidelity.

Box 1: Details of assessment of the medical record review and intervention fidelity

Medical record review for deceased patients

Trained members of the research team will consider all of a patient's available medical records (at the acute hospital where they receive their oncology care) to assess concordance between documentation of preferences for care and medical interventions received, place of death and timing and location of documentation of EOL preferences (secondary outcomes A,B and C). Reviewers will receive two days of face face to face group training, and be provided with a standard form and written guidelines. 10% of records will be re-abstracted by a second reviewer to assess for Inter-Rater Reliability. Reviewers will have real-time consultation with medically trained staff if required. Where the abstractor is unsure of how to score, cases will be referred first to the study coordinator and then to the steering committee for additional review until consensus is reached.

Intervention fidelity

All intervention sessions will be audio recorded. This provides an opportunity to assess how the intervention was actually delivered in practice. There are currently no tools available which aim to measure the quality and consistency of ACP interventions. Additionally, there have been no published reports of auditing actual practice of ACP inside of a clinical trial setting. We will use the data from the recorded ACP conversations to: (1) Design and evaluate a fidelity instrument; (2) Describe variations in ACP intervention delivery; and (3) Analyse correlations between delivery with patient outcomes.

Sample size

In a previous trial by the investigator group EOL wishes were known and respected in 86% of the intervention group compared to 30% of controls [14]. Assuming the same baseline rate of EOL wishes known and respected in cancer patients, and believing a doubling to 60% would influence clinical practice, two study groups that each include 56 patients who die within the 3 year follow up period will result in the study having 90% power to detect a between-group difference with 95% certainty. A conservative estimate of mortality is 75%. To allow for incomplete data on 20% of patients and a further 10% of their nominated family members or friends, we propose a sample size of 210 patients with advanced incurable cancer.

Recruitment and Randomisation

Oncologists at participating sites will be asked to identify patients who meet the study inclusion criteria and to inform patients about the study during their outpatient oncology visits. Potential participants will be introduced to a research team member in attendance at the clinic who will provide them with further details of the study.Family members or friends who are not in attendance at the clinic will receive a follow up phone call from the research team. The information provided in the consent form will be the same for the intervention group and the control group. The information sheets will exclude naming the intervention (Advance Care Planning) in order to avoid contamination of the control arm. Participants will be informed that the project is evaluating the effectiveness of a program aimed at improving communication with patients with advanced cancer, their family and friends and their doctors. Participants will be informed that those randomised to the intervention group will meet with a specially trained nurse to talk through their goals, wishes and needs for care now and in the future. Participants in this study will be advised before entry that participation is voluntary and they are free to withdraw at any time.

Participants will be randomised by minimisation with a 1:1 allocation of control group to intervention group. Participants will be stratified by site and gender, using the 24/7 IVRS (Interactive Voice Response System) telephone based randomisation system at the National Health and Medical Research Council (NHMRC) Clinical Trials Centre.

The statistical analysis and preparation of tables and graphs for the report of the study by the statistician of the study will be blinded. Research staff completing follow up assessment and medical record review will be blinded to the extent possible (participants will be identifiable by study ID only, but the 8 week assessment contains additional 'satisfaction with the intervention' questionnaire for intervention participants and the medical record may include study specific documents). Participants and oncologists will be non-blinded.

Statistical analysis

The study statistician performing the analysis will be blinded to group allocation. The effect of the ACP intervention will be assessed by using chi-squared tests for categorical outcomes and t-tests for continuous outcomes, if measured at one time point only and if there is no oncologist effect. Clustering by oncologist will be tested using mixed models, and if the intra-cluster correlation is estimated to be non-zero, outcomes will be analysed using mixed models and generalised linear mixed models with oncologist included as a random effect. Outcomes which are measured repeatedly (e.g. QoL, satisfaction with care) will be analysed with mixed models, to assess patterns over time as well as differences between group at specific time points. These models are valid for data that are missing completely and missing at random [24] . All analyses will follow the intention to treat. Mixed models are consistent with an intention to treat analysis in the presence of missing data [25] . A secondary per-protocol analysis will be performed along

with an exploration of why any participants did not receive the treatment to which they were assigned. Accuracy of predictions of survival time will be investigated using descriptive statistics and Bland-Altman plots [26] for those patients who die within the follow up period. Differences in survival will be explored with Kaplan Meier plots.

Descriptive statistics will be used to describe the sample and to compare the characteristics of patients in the different groups.

Interim analyses plan

Analysis of satisfaction with intervention and QOL data will be undertaken at mid-point of the study to ensure no adverse consequences.

Data monitoring plan

The study steering committee will monitor the course of the trial and provide ongoing oversight of the preliminary results. Investigators will review un-blinded results and if necessary will give a recommendation for discontinuation, modification or continuation of the study.

DISCUSSION

The study has several strengths and limitations which are described below.

Strengths

The study design follows that of a previous randomised controlled trial conducted by members of the investigator team [14]. Therefore both the study protocol and intervention have been proven to be feasible and successful in a different patient population. Furthermore, the ACP intervention used in the present study has a number of specific strengths. Firstly, it includes both patients and their family member or friend. Secondly, the ACP intervention is available to participants assigned to intervention for as many sessions as they request. Thirdly the ACP intervention has been adapted to be cancer specific and lastly the intervention includes optional provision of and discussion of prognostic information. The study also has methodological strengths. The ACP study is a randomised controlled trial with allocation concealed using a computer generated interactive voice system in order to prevent systematic bias.

Limitations

The proportion of eligible patients who participate in the trial will be documented. It is likely that there will be systematic differences between those who choose to participate in the ACP trial and those who choose not to participate. Secondly, it is likely that completing study questionnaires will prompt some participants in both arms of the study to consider and discuss their end of life wishes. Thirdly, it is unavoidable that in conducting a longitudinal study involving patients with incurable disease a number of participants will die before follow up data can be collected, withdraw from the study or be lost to follow up. Fourth, the study intervention is complex and requires skill, time and resources to deliver. It may be difficult to replicate consistently across institutions.

Lastly, as the ACP intervention requires the involvement of treating oncologists and documentation in the medical record both the oncologists and researchers working in the study cannot be blinded to group allocation.

Two other RCT's are underway, which also investigate the effects of ACP in cancer [27 28]. This presents an opportunity for meta-analysis of data on the effectiveness of ACP in cancer care. Data will be collected for almost 2000 advanced cancer patients across Europe, The USA and Australia. Shared patient outcomes across all three studies include: concordance with EOL wishes and care received, quality of communication, quality of death/Quality of end of life care, patient mental health outcomes and acceptability of the ACP intervention. Further details of each study are presented in Table 3. However, there are no gold standard outcomes, or measures to assess the efficacy of ACP, and a variety of measures will be used across studies to assess similar outcomes. This presents a challenge to meta-analysis. Table 3 presents details of study design, sample size, population, intervention and primary outcome measure for each study. Shared patient outcomes and a brief description of the distinguishing features between studies are also presented. A full list of the outcome measures used in each study can be found in the published study protocols[27 28]

Table 3: Details and comparison between three RCT's of ACP in cancer care

Study name	Study design	Sample size	Population	Intervention	Primary outcome	Shared patient outcomes	Distinguishing features of each study*
ACTION Study[28]	Cluster RCT	1334	Patients with advanced lung or colorectal cancer	Adapted Respecting Patient Choices model	Quality of Life	Goal concordant care Quality of life Quality of death / quality of end of life care Satisfaction with the intervention Timing, place and prevalence of documentation about EOLC	Shared decision making/Patient involvement/ Coping with illness Qualitative study of patients, relative and professional caregivers experiences of involvement in ACP
Bernacki[27]	Cluster RCT	426	Patients with advanced incurable cancer and a life expectancy of less than 12 months	A multi-component, structured communication intervention	Receipt of goal-concordant care, and peacefulness at the EOL		Clinician outcome data – attitudes, confidence, acceptability, prognostic evaluation
Australian ACP study	One to one randomisation RCT	210	Patients with advanced cancer, and a life expectancy of 3-12 months	Adapted Respecting Patient Choices model + prognostic information	Family or friend reported: a) discussion with the patient about their EOL wishes and b) perception that the patient's EOL wishes were met	Place of death Resource use/cost analysis	Estimating and discussing survival scenarios Bereavement outcomes for family/friends

ETHICS AND DISSEMINATION

This study is funded by The National Health and Medical Research Council (grant number APP 1050596) and is administered through the University of Sydney. There are no contractual agreements that limit data access for investigators. The study sponsor will have no no role in the study design; collection, management and interpretation of data; writing of reports; and the decision to submit reports for publication.

The study will be conducted in accordance with the National Health and Medical Research Council's guidelines for the ethical conduct of human research. The study investigator team which includes academics and clinicians with a broad range of skills and experience, has been established as a steering committee. The steering committee meet quarterly and will guide study procedures and dissemination of results. Important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) will be communicated to relevant parties via regular study newsletters. The steering committee will also be responsible for assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct.

All information collected during the course of the study will be kept strictly confidential and any information which would allow individual participants to be identified will not be released. Anonymised data will be compared; individual patients, family members or oncologists will not be identifiable." The results will be submitted for publication in peer-reviewed journals and will be presented at national and international conferences. The results of this study will provide evidence for the direction and development of quality EOL care for patients with advanced cancer.

ABBREVIATIONS

ACP Advance care planning

EOL End of life

QOL Quality of Life

COMPETING INTERESTS

The author(s) declare that they have no competing interests

AUTHOR'S CONTRIBUTIONS

Stephanie Johnson is the study coordinator and drafted the manuscript. All authors contributed to the study design and review of the manuscript.

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Figure 1: Core components of the ACP intervention

I.	Negotiate an agenda for the consultation
II.	Assess the patient's and/or family's readiness to discuss future care
III.	Explore the patient's understanding of their medical situation, any unmet information needs and provide information if appropriate
IV.	Explore the patient's values, goals, priorities, hopes, fears and concerns for the future
V.	Explore if there are any situations, treatments or health states the patient would find unacceptable
VI.	Summarise your understanding of the person's most important wishes for future care
VII.	Consider any other specific treatment options relevant to the person's circumstances
VIII.	Consider offering to make a recommendation for future medical care, if they were to become too sick to speak for themselves, based on their values and wishes
IX.	Help the patient to document their wishes

Figure 1: Core components of the ACP intervention

151x133mm (300 x 300 DPI)

Figure 2: Participant assessment and follow up plan

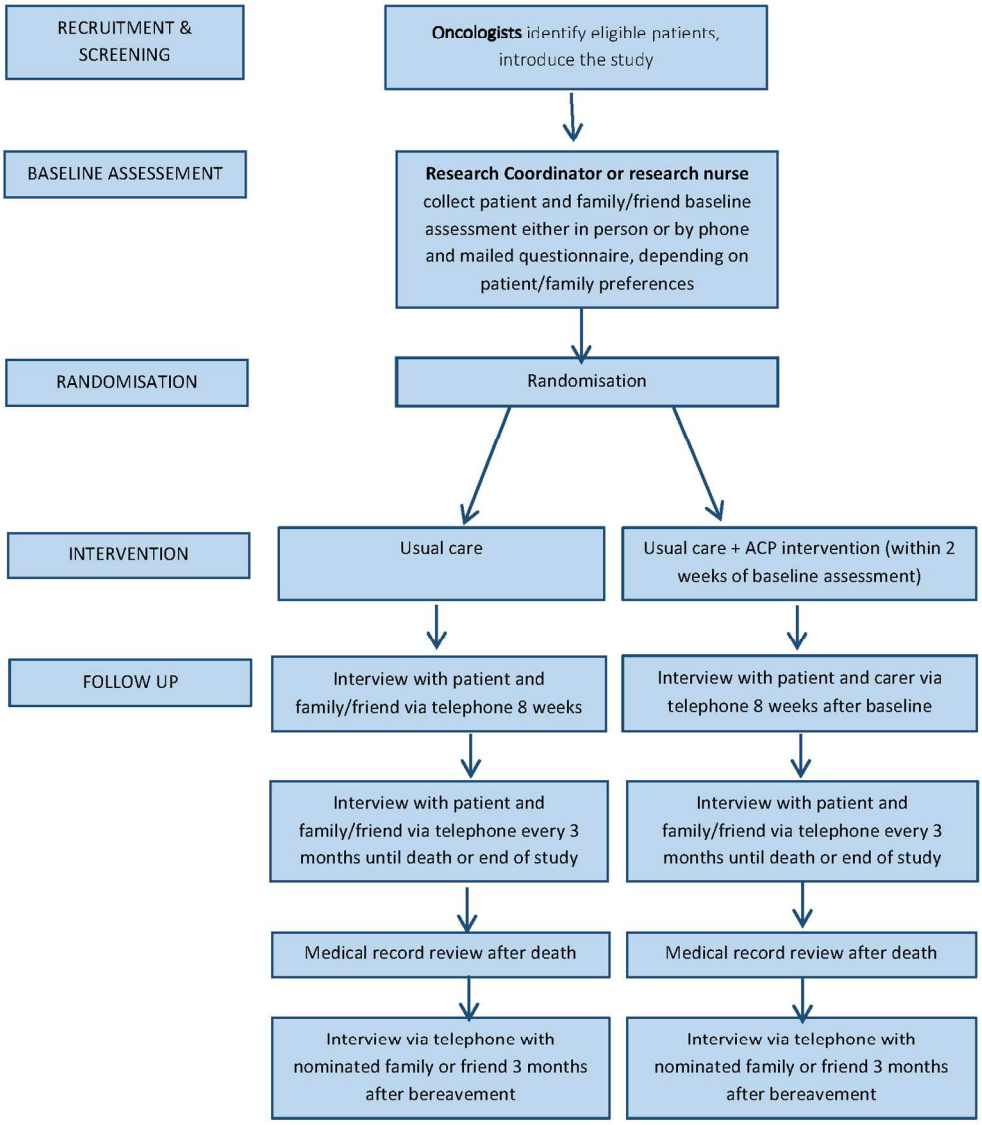

Figure 2: Participant assessment and follow up plan

143x172mm (300 x 300 DPI)

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
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym – Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry – Page 2
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier – title page of protocol
Funding	4	Sources and types of financial, material, and other support – Page 2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors – Page 2
	5b	Name and contact information for the trial sponsor– Page 2
	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 – Page 13
	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) – Page 12
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 – Page 3
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses – Page 3 and 4

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) – Page 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 – Page 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) – Page 4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered – Page 5
	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) – Page 5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Box 1 (page 5)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial N/A
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 – Page 7
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) – Page 6. Figure 2, Table 1 and 2
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 – Page 9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size – Page 9
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 – Page 9
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 – Page 9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions – Page 9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how– Page 9
	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 – Page 7 – 10
	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 – Page 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 – Page 5
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 – Page 10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) – Page 10
	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)

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 – Page 11
	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 – Page 10
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 – Page 13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor – Page 12
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval – Page 12
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) – Page 12
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) – Page 9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable– NA
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– Page 12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site – Page 13
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 –Page 13
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-NA

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 – Page 12
	31b	Authorship eligibility guidelines and any intended use of professional writers NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code NA
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.