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A pre-consultation compassion intervention to reduce anxiety among patients referred to a cancer center: protocol for a randomized control trial

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A pre-consultation compassion intervention to reduce anxiety among patients referred to a cancer center: protocol for a randomized control trial

Version 1
12/17/20

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Abstract

Introduction: Patients diagnosed with cancer commonly have a high degree of anxiety during an initial oncology consultation, which may interfere with a patient's ability to retain information required to make informed treatment decisions. A previous study randomized breast cancer survivors (volunteers) to view either (a) a brief video depicting a standard initial consultation from an oncologist or (b) an identical consultation with the addition of compassionate statements from the oncologist, and found the compassionate statements reduced anxiety among the volunteers. However, while compassionate statements reduced anxiety during simulation, it is currently unknown if watching a video containing compassionate statements from an oncologist prior to an initial oncology consultation will reduce anxiety among patients referred to a cancer center. The aim of this randomized control trial is to test if watching a brief video containing compassionate statements from an oncologist, compared to watching a standard introduction video, prior to an initial oncology consultation will reduce the degree of anxiety among patients referred to a cancer center.

Methods and analysis: This is a prospective, randomized controlled clinical trial at an academic cancer center. We will enroll adult patients scheduled for an initial oncology consultation. Subjects will be randomly assigned to receive a standard introduction video or enhanced compassion video for viewing prior to the initial oncology consultation. On arrival to the cancer center we will measure anxiety severity using the Hospital Anxiety and Depression scale (HADS). The HADS has two 7-item subscales (HADS Anxiety and HADS Depression) and is well-validated among oncology patients. We will use Wilcoxon rank-sum test to test for a difference in the HADS subscales between the two video groups.

Ethics and dissemination: The local Institutional Review Board approved this study. The results from this randomized control trial will be submitted for publication to a peer-reviewed journal.

Registration: NCT04503681

Word count: 298

Keywords: Compassion, empathy, anxiety, depression, cancer, oncology

Strengths:

- This study is the first to test if viewing an enhanced compassion video prior to an initial oncology consultation reduces anxiety among patients referred to a cancer center.
- The study design will enroll patients across a diverse spectrum of cancer diagnoses allowing for greater generalizability of results.

Limitations:

- The study protocol may result in a proportion of the potential subjects undergoing randomization but not being exposed to the interventions (i.e. deciding not to watch or unable to watch the videos) resulting in a null experiment.

Introduction

During an initial oncology consultation, when clinicians are discussing cancer diagnosis and treatment options, it is common for patients to have a high degree of anxiety.[1,2] Not only is anxiety psychologically distressing, but also anxiety is a common reason for patients not attending (i.e. "no show") urgent referral appointments for suspected cancer.[3] In addition, a high degree of anxiety has been shown to compete with task-relevant processes and restrict the capacity of working memory.[4] Therefore, anxiety may interfere with a patient's ability to retain information and attenuate a patient's ability to make informed treatment decisions. Perhaps more concerning, anxiety among patients with cancer is associated with increased mortality; while alternatively anxiety treatment is associated with reduced mortality risk.[5] Interventions aimed at reducing anxiety among patients with suspected cancer may allow for enhanced patient involvement in care, improved quality of life, and improved outcomes.

A previous study by Fogarty, *et al* randomized breast cancer survivors (volunteers) to watch one of two different videos.[6] The standard video was a dramatized oncologist-breast cancer patient consultation in which a physician described two treatment options for metastatic breast cancer. The second "enhanced compassion" video was identical to the standard video, but also included two additional segments, during which the oncologist acknowledged the psychological concerns of the patient, validated the patient's emotional state, and expressed emotional support. They found that the breast cancer survivor volunteers who watched the enhanced compassion video had a significantly lower degree of anxiety compared to the group who watched the standard video. Although compassionate statements significantly reduced anxiety among the volunteers who watched the simulated video, it is currently unknown if the same intervention would reduce anxiety among active cancer patients undergoing an initial consultation. The primary aim of this randomized control trial is to test if watching a video containing compassionate statements from an oncologist, compared to watching a standard introduction video, prior to an initial oncology

consultation will reduce the degree of anxiety among patients referred to a cancer center. In addition, we will test if the enhanced compassion video reduces the patient no-show rate for the initial oncology consultation. We hypothesize that among patients referred to a cancer center for suspected cancer, watching a video containing compassionate statements from an oncologist prior to the initial cancer consultation will reduce patient anxiety and no-show rate compared to watching a standard introduction video.

Methods and analysis

Protocol and registration

This randomized control trial protocol was prepared in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.[7,8] The final results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement.[9] This randomized control trial has been registered on the United States National Library of Medicine ClinicalTrials.gov (NCT04503681).

Study design

This study is a prospective, randomized, controlled, parallel-group clinical trial at a single university-based cancer center (MD Anderson Cancer Center at Cooper, Cooper University Health Care, Camden, New Jersey, USA). Enrollment is anticipated to occur between May 1st and July 31st, 2021. Potential subjects will be enrolled at the time of scheduling an initial cancer consultation. Our Institutional Review Board allowed alteration of the requirements of obtaining informed consent under 45 CFR 46.116(d) given the intervention was deemed no greater than minimal risk. All new adult patients scheduled for an initial cancer consultation at MD Anderson Cancer Center at Cooper will be randomized to receive an email containing a link for either the "standard introduction video" or the "enhanced compassion video." Emails will be sent to patients prior to obtaining informed consent to allow for viewing of the video prior to the initial oncology consultation and to keep the patients masked to the study hypotheses prior to the consultation. When the patients arrive to the Cancer Center waiting room for his/her initial cancer consultation they will be approached by research staff to obtain written informed consent to complete the research questionnaire and for use of data.

Participants

We will enroll adult patients scheduled for an initial cancer consultation at MD Anderson Cancer Center at Cooper. Inclusion criteria include: 1) age ≥ 18 years; 2) scheduled for an initial cancer consultation. We will exclude patients who do not have an active email address or are medically unable to complete the research questionnaire at the time of the initial cancer consultation.

Randomization and masking

Patients will be randomly assigned to one of two groups, standard introduction video or enhanced compassion video. An independent statistician will generate the group assignment sequence using a parallel design, 1:1 randomization schedule. Standard measures will be used to ensure appropriate concealment of group assignment. The randomization assignments will be kept in a sequential list and maintained in the scheduling operator office. At the time of scheduling an initial consultation, appointment operators will identify the next assignment in the series, which will be labeled either “Video A” or “Video B.” The operators will then send the appropriate email containing a link to a website for the matching video. The independent statistician will maintain the code link for the videos. Thus, the operators, investigators, and research statistician will be blinded to video allocation until after all study analyses have been completed.

*Intervention*s

As part of a currently ongoing clinical quality initiative at our institution, when a new patient schedules an appointment for an initial cancer consultation the scheduling operator sends an email to the patient containing a link for a standard introduction video (see script below). For the purposes of this study a second enhanced compassion video was developed, which added five additional sentences to the standard introduction video. Those five sentences were compassion-focused statements. Both videos feature the same oncologist (i.e. Medical Director

of MD Anderson Cancer Center at Cooper) and are identical aside from the additional compassionate statements. The compassionate statements added to the enhanced compassion video were based on the statements used in the Fogarty, *et al* study,[6] and further modified based on the results of a recent systematic review of clinician compassionate behaviors, which found incorporating statements of support, acknowledgement, patient's perspective, emotion naming, and validation increased patient perception of compassion.[10]

Script for the standard introduction video:

"Hello, I'm Dr. X, Medical Director of MD Anderson Cancer Center at Cooper.

Thank you for choosing MD Anderson at Cooper. We value your confidence in our team.

We believe that exceptional treatment requires a team of experts who specialize in a specific type of cancer. We call this multidisciplinary care. This means that cancer specialists work together to develop and deliver a personalized care plan just for you.

Our nurse navigators are important members of our team. Your nurse navigator will educate you about your diagnosis and treatment, and help guide you throughout your journey – answering your questions and putting you in touch with the services you need.

We encourage you to be an active participant in your care. Ask questions, take notes during your visits, and take advantage of the many different supportive care services we have available to you – like our complementary medicine therapies, nutrition counseling, and social work services.

Once again, thank you for choosing MD Anderson at Cooper for your care."

Script for the enhanced compassion video (added compassion statements marked with **):

"Hello, I'm Dr. X, Medical Director of MD Anderson Cancer Center at Cooper.

Thank you for choosing MD Anderson at Cooper. We value your confidence in our team.

We know a cancer diagnosis is a tough experience to go through, and I want you to know that we are here with you. Some of the things said during your upcoming visit may be difficult to understand, and we want you to feel comfortable with asking questions if something is confusing or doesn't make sense. We will be with you, and we will go through this together.

We believe that exceptional treatment requires a team of experts who specialize in a specific type of cancer. We call this multidisciplinary care. This means that cancer specialists work together to develop and deliver a personalized care plan just for you.

Our nurse navigators are important members of our team. Your nurse navigator will educate you about your diagnosis and treatment, and help guide you throughout your journey – answering your questions and putting you in touch with the services you need.

We encourage you to be an active participant in your care. Ask questions, take notes during your visits, and take advantage of the many different supportive care services we have available to you – like our complementary medicine therapies, nutrition counseling, and social work services.

I know this is a tough time for you, and I want to emphasize again that we are in this together. We will be with you each step along the way.

Once again, thank you for choosing MD Anderson at Cooper for your care."

Measurements and Data Collection

After obtaining written informed consent we will administer a research questionnaire to patients at the cancer center prior to the initial cancer consultation. The questionnaire will assess the patients' perception of the video oncologist's compassion using the 5-item compassion measure, a previously validated patient-assessed measure of perceived compassion during patient care.[11,12] We will abstract patient demographics, as well as clinical information pertaining to cancer diagnosis from the medical record.

Outcome measures

The primary outcome measure will be anxiety severity on arrival to the cancer center for the initial consultation. As part of the research questionnaire patients will be asked to complete the Hospital Anxiety and Depression scale (HADS). The HADS is a 14-item self-reported instrument that assesses anxiety and depressive symptoms in populations with medical conditions (both in- and out-patients).[13,14] It has two 7-item subscales: HADS Anxiety and HADS Depression. Each item is scored on a 4-point scale (0=not at all to 3=nearly all the time); thus, each sub-scale can range from 0–21. The HADS has been extensively validated in oncology populations, and is a commonly used measure of anxiety and depression in oncology studies.[15-18] The HADS Depression score will be analyzed as a secondary outcome. As an additional secondary

outcome measure we will determine the no-show rate for the initial consultation among each group. We will enter all data into Research Electronic Data Capture (REDCap), a secure, web-based application designed to support data capture for research studies,[19] and export the data into Stata/SE 16.1 for Mac, StataCorp LP (College Station, TX, USA) for analysis.

Statistical analysis

For descriptive statistics we will report categorical data as proportions with 95% confidence intervals and continuous data as means with standard deviations or medians with interquartile ranges as appropriate. As part of the CONSORT diagram[9] we will report the proportion of patients who do not attend their initial cancer consultation, as well as the proportion of patients who attend their initial consultation, but decline to participate in the study, stratified by video group allocation. We will test if the enhanced compassion video reduced the no-show rate to the initial consultation, as well as increased participation in research using the Fisher exact test. We will use Cronbach's alpha to separately test the internal reliability of the HADS anxiety scale, HADS depression scale, and the 5-item compassion measure among our cohort. We will test if the enhanced compassion video group perceived the video oncologist as more (or less) compassionate, as measured by the 5-item compassion measure, than the standard introduction video group using the Wilcoxon rank-sum test.

For the primary outcome, we will use the Wilcoxon rank-sum test to test for a difference in the HADS anxiety scale between the two video groups. We will also perform a sensitivity analysis dichotomizing the HADS anxiety scale into low (< 8) and moderate/high (≥ 8). A cut point of 8 on the HADS subscales has been defined as the optimal cut point for diagnosis screening and is commonly used to define clinically significant symptoms in research studies.[16,20] We will use the Fisher exact test, to test if the proportion of patients with clinically significant symptoms differed between the two video groups. For our secondary outcome measure we will repeat the same

analyses described above using the HADS depression scale in place of the HADS anxiety scale. We will perform the above analyses using intention to treat methodology. The analyses will be repeated in a per protocol fashion excluding patients who state they did not watch the video prior to presentation to the cancer center.

To test if the relationship between video group and anxiety severity differs among pre-specified subgroups we will perform separate multivariable linear regression models with the HADS anxiety scale as the dependent variable, and entering the following patient characteristic along with an interaction term between video group and the characteristic as independent variables: (1) age (decile), (2) sex (male vs. female), (3) race (white vs. non-white), (4) ethnicity (Hispanic vs. non-Hispanic), (5) suspected primary cancer (breast vs. gastrointestinal vs. pulmonary vs. skin vs. central nervous system vs. gynecologic vs. other).

Sample Size calculation

Assuming an alpha of 0.05, power of 0.8, and a standard deviation of 5 for the HADS anxiety scale, based on previous literature,[15,17] in order to detect a clinical meaningful difference (previously defined as a 1.5-point difference)[21] between subjects who viewed the standard introduction video compared to subjects who viewed the enhanced compassion video we will need 176 subjects per group. Assuming a 25% lost to follow-up (i.e. non-attendance to consultation or decline to participate), to ensure accrual of the total sample size of 352, we plan to enroll 470 total subjects.

Protocol amendments

Any amendments to this protocol will be described along with the rationale and date the change was implemented.

Patient and Public Involvement

We designed this study given previous research has demonstrated that compassionate patient care is considered one of the most important aspects of high quality healthcare by patients and patient family members.[22,23] However, individual patients were not involved in the design of this study.

Data sharing

After review and approval by our study data use committee, we will allow other researchers who submit to us a suitable protocol to have access to the complete de-identified datasets used and/or analyzed during the study, in comma separated value format together with a data dictionary.

Ethics and dissemination

As stated above this study was approved by the Cooper University Health Care Institutional Review Board with alteration of the requirements of obtaining informed consent under 45 CFR 46.116(d). The results from this randomized control trial will be submitted for publication to peer-reviewed journals, and to national meetings in presentation form.

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Author's contributions

All authors have made substantial contributions to this report and have satisfied International Committee of Medical Journal Editors (ICMJE) criteria for authorship. BWR supervised all aspects of the study design and takes responsibility for the paper as a whole. All authors contributed to the study design, and development of the video scripts. BWR provided statistical expertise. BWR, CCW, and ST drafted the manuscript. All authors read and contributed substantially to revision of the final manuscript. All authors approved the manuscript in its final form.

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Competing interest statement

Drs. Trzeciak and Mazzarelli are co-authors of a book on compassion science entitled "Compassionomics". None of the other authors have disclosures.

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____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	____Page 1_____
Funding	4	Sources and types of financial, material, and other support	_Page 16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Pages 1 and 16
	5b	Name and contact information for the trial sponsor	__N/A___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_N/A___
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_N/A_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 4
	6b	Explanation for choice of comparators	Page 4
Objectives	7	Specific objectives or hypotheses	Page 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 6
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 6
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 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Pages 7-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	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	Pages 9-10
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)	Pages 6-7

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 11_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Pages 6-7_____
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 7_____
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 7_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_Page 7_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 7_____
	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	Pages 9-10_____
	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	Pages 9-10_____

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 10_____
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	Pages 10-11___
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_Pages 10-11__
	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)	Page 11_____
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	N/A_____
	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	N/A_____
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	N/A_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_Page 6_____
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 11_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_Page 16
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 12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 12
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplemental
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__N/A

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

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A pre-consultation compassion intervention to reduce anxiety among patients referred to a cancer center: protocol for a randomized control trial

Version 2
4/18/21

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Abstract

Introduction: Patients diagnosed with cancer commonly have a high degree of anxiety during an initial oncology consultation, which may interfere with a patient's ability to retain information required to make informed treatment decisions. A previous study randomized breast cancer survivors (volunteers) to view either (a) a brief video depicting a standard initial consultation from an oncologist or (b) an identical consultation with the addition of compassionate statements from the oncologist, and found the compassionate statements reduced anxiety among the volunteers. However, while compassionate statements reduced anxiety during simulation, it is currently unknown if watching a video containing compassionate statements from an oncologist prior to an initial oncology consultation will reduce anxiety among patients referred to a cancer center. The aim of this randomized control trial is to test if watching a brief video containing compassionate statements from an oncologist, compared to watching a standard introduction video, prior to an initial oncology consultation will reduce the degree of anxiety among patients referred to a cancer center.

Methods and analysis: This is a prospective, randomized controlled clinical trial at an academic cancer center. We will enroll adult patients scheduled for an initial oncology consultation. Subjects will be randomly assigned to receive a standard introduction video or enhanced compassion video for viewing prior to the initial oncology consultation. On arrival to the cancer center we will measure anxiety severity using the Hospital Anxiety and Depression scale (HADS). The HADS has two 7-item subscales (HADS Anxiety and HADS Depression) and is well-validated among oncology patients. We will use Wilcoxon rank-sum test to test for a difference in the HADS subscales between the two video groups.

Ethics and dissemination: The Cooper University Hospital Institutional Review Board approved this study. The results from this randomized control trial will be submitted for publication to a peer-reviewed journal.

Registration: NCT04503681

Word count: 200

Keywords: Compassion, empathy, anxiety, depression, cancer, oncology

Strengths:

- This study is the first to test if viewing an enhanced compassion video prior to an initial oncology consultation reduces anxiety among patients referred to a cancer center.
- The study design will enroll patients across a diverse spectrum of cancer diagnoses allowing for greater generalizability of results.

Limitations:

- The study protocol may result in a proportion of the potential subjects undergoing randomization but not being exposed to the interventions (i.e. deciding not to watch or unable to watch the videos) resulting in a null experiment.
- Given the study design, subjects without an active email address will be excluded potentially limiting generalizability of the study results.

Introduction

During an initial oncology consultation, when clinicians are discussing cancer diagnosis and treatment options, it is common for patients to have a high degree of anxiety.[1,2] Not only is anxiety psychologically distressing, but also anxiety is a common reason for patients not attending (i.e. "no show") urgent referral appointments for suspected cancer,[3] with approximately 5-7% of referred patients not attending their scheduled appointment.[4] In addition, a high degree of anxiety has been shown to compete with task-relevant processes and restrict the capacity of working memory.[5] Therefore, anxiety may interfere with a patient's ability to retain information and attenuate a patient's ability to make informed treatment decisions. Perhaps more concerning, anxiety among patients with cancer is associated with increased mortality; while alternatively anxiety treatment is associated with reduced mortality risk.[6] Interventions aimed at reducing anxiety among patients with suspected cancer may allow for enhanced patient involvement in care, improved quality of life, and improved outcomes.

Compassion is commonly defined as the emotional response to another's pain or suffering involving an authentic desire to help.[7-9] Clinician compassion can be conveyed to patients through patient-centered communication, which has been shown to be associated with better patient emotional health.[10] During consultation, clinician assessment of the patient's feelings and concerns, in addition to the physical aspects of the patient's ailment, is positively associated with patient emotional health and symptom resolution.[11] In addition, compassionate communication is viewed by patients as an vital component of the clinician-patient relationship.[12] Previous studies have found when volunteers watch video-vignettes of clinician-patient interactions, videos containing compassionate statements increase volunteer trust in the physician and overall satisfaction, as well as decrease volunteer uncertainty and anxiety.[13,14] A study by Fogarty, *et al* randomized breast cancer survivors (volunteers) to watch one of two different videos.[15] The standard video was a dramatized oncologist-breast cancer patient

consultation in which a physician described two treatment options for metastatic breast cancer. The second “enhanced compassion” video was identical to the standard video, but also included two additional segments, during which the oncologist acknowledged the psychological concerns of the patient, validated the patient’s emotional state, and expressed emotional support. They found that the breast cancer survivor volunteers who watched the enhanced compassion video had a significantly lower degree of anxiety compared to the group who watched the standard video. Although compassionate statements significantly reduced anxiety among the volunteers who watched the simulated video, it is currently unknown if the same intervention would reduce anxiety among active cancer patients undergoing an initial consultation.

The primary aim of this randomized control trial is to test if watching a video containing compassionate statements from an oncologist, compared to watching a standard introduction video (sent as part of an ongoing clinical quality initiative at our institution), prior to an initial oncology consultation will reduce the degree of anxiety among patients referred to a cancer center. In addition, we will test if the enhanced compassion video reduces the patient no-show rate for the initial oncology consultation. We hypothesize that among patients referred to a cancer center for suspected cancer, watching a video containing compassionate statements from an oncologist prior to the initial cancer consultation will reduce patient anxiety and no-show rate compared to watching a standard introduction video.

Methods and analysis

Protocol and registration

This randomized control trial protocol was prepared in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.[16,17] The final results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement.[18] This randomized control trial has been registered on the United States National Library of Medicine ClinicalTrials.gov (NCT04503681).

Study design

This study is a prospective, randomized, controlled, parallel-group clinical trial at a single university-based cancer center (MD Anderson Cancer Center at Cooper, Cooper University Health Care, Camden, New Jersey, USA). Enrollment is anticipated to occur between May 1st and July 31st, 2021. Potential subjects will be enrolled at the time of scheduling an initial cancer consultation. Our Institutional Review Board allowed alteration of the requirements of obtaining informed consent under 45 CFR 46.116(d) given the intervention was deemed no greater than minimal risk. All new adult patients scheduled for an initial cancer consultation at MD Anderson Cancer Center at Cooper will be randomized to receive an email containing a link for either the "standard introduction video" or the "enhanced compassion video." Emails will be sent to patients prior to obtaining informed consent to allow for viewing of the video prior to the initial oncology consultation. The study will not be discussed with patients prior to their scheduled appointment in order to keep the patients masked to the study hypotheses prior to the consultation and to prevent any influence knowledge of the videos' purpose may have on the outcome measures. When the patients arrive to the Cancer Center waiting room for his/her initial cancer consultation they will be approached by research staff to obtain written informed consent (**Supplementary File**) to complete the research questionnaire and for use of data. All appointments will take place in the office (i.e. no telemedicine appointments).

Participants

We will enroll adult patients scheduled for an initial cancer consultation at MD Anderson Cancer Center at Cooper. Inclusion criteria include: 1) age ≥ 18 years; 2) scheduled for an initial cancer consultation. We will exclude patients who do not have an active email address or are medically unable to complete the research questionnaire at the time of the initial cancer consultation.

Randomization and masking

Patients will be randomly assigned to one of two groups, standard introduction video or enhanced compassion video. An independent statistician will generate the group assignment sequence using a parallel design, 1:1 randomization schedule. Standard measures will be used to ensure appropriate concealment of group assignment. The randomization assignments will be kept in a sequential list and maintained in the scheduling operator office. At the time of scheduling an initial consultation, appointment operators will identify the next assignment in the series, which will be labeled either “Video A” or “Video B.” The operators will then send the appropriate email containing a link to a website for the matching video. The independent statistician will maintain the code link for the videos. Thus, the operators, investigators, and research statistician will be blinded to video allocation until after all study analyses have been completed.

*Intervention*s

As part of a currently ongoing clinical quality initiative at our institution, when a new patient schedules an appointment for an initial cancer consultation the scheduling operator sends an email to the patient containing a link for a standard introduction video (see script below). For the purposes of this study a second enhanced compassion video was developed, which added five additional sentences to the standard introduction video. Those five sentences were

compassion-focused statements. Both videos feature the same oncologist (i.e. Medical Director of MD Anderson Cancer Center at Cooper) and are identical aside from the additional compassionate statements. The compassionate statements added to the enhanced compassion video were based on the statements used in the Fogarty, *et al* study,[15] and further modified based on the results of a recent systematic review of clinician compassionate behaviors, which found incorporating statements of support, acknowledgement, patient's perspective, emotion naming, and validation increased patient perception of compassion.[19]

Script for the standard introduction video:

"Hello, I'm Dr. X, Medical Director of MD Anderson Cancer Center at Cooper.

Thank you for choosing MD Anderson at Cooper. We value your confidence in our team.

We believe that exceptional treatment requires a team of experts who specialize in a specific type of cancer. We call this multidisciplinary care. This means that cancer specialists work together to develop and deliver a personalized care plan just for you.

Our nurse navigators are important members of our team. Your nurse navigator will educate you about your diagnosis and treatment, and help guide you throughout your journey – answering your questions and putting you in touch with the services you need.

We encourage you to be an active participant in your care. Ask questions, take notes during your visits, and take advantage of the many different supportive care services we have available to you – like our complementary medicine therapies, nutrition counseling, and social work services.

Once again, thank you for choosing MD Anderson at Cooper for your care."

Script for the enhanced compassion video (added compassion statements marked with **):

"Hello, I'm Dr. X, Medical Director of MD Anderson Cancer Center at Cooper.

Thank you for choosing MD Anderson at Cooper. We value your confidence in our team.

We know a cancer diagnosis is a tough experience to go through, and I want you to know that we are here with you. Some of the things said during your upcoming visit may be difficult to understand, and we want you to feel comfortable with asking questions if something is confusing or doesn't make sense. We will be with you, and we will go through this together.

We believe that exceptional treatment requires a team of experts who specialize in a specific type of cancer. We call this multidisciplinary care. This means that cancer specialists work together to develop and deliver a personalized care plan just for you.

Our nurse navigators are important members of our team. Your nurse navigator will educate you about your diagnosis and treatment, and help guide you throughout your journey – answering your questions and putting you in touch with the services you need.

We encourage you to be an active participant in your care. Ask questions, take notes during your visits, and take advantage of the many different supportive care services we have available to you – like our complementary medicine therapies, nutrition counseling, and social work services.

I know this is a tough time for you, and I want to emphasize again that we are in this together. We will be with you each step along the way.

Once again, thank you for choosing MD Anderson at Cooper for your care."

Measurements and Data Collection

After obtaining written informed consent we will administer a research questionnaire to patients at the cancer center prior to the initial cancer consultation. The questionnaire will assess the patients' perception of the video oncologist's compassion using the 5-item compassion measure, a previously validated patient-assessed measure of perceived compassion during patient care.[20,21] We will abstract patient demographics, as well as clinical information pertaining to cancer diagnosis from the medical record.

Outcome measures

The primary outcome measure will be anxiety severity on arrival to the cancer center for the initial consultation. As part of the research questionnaire patients will be asked to complete the Hospital Anxiety and Depression scale (HADS). The HADS is a 14-item self-reported instrument that assesses anxiety and depressive symptoms in populations with medical conditions (both in- and out-patients).[22,23] It has two 7-item subscales: HADS Anxiety and HADS Depression. Each item is scored on a 4-point scale (0=not at all to 3=nearly all the time); thus, each sub-scale can range from 0–21. The HADS has been extensively validated in oncology populations, and is a commonly used measure of anxiety and depression in oncology studies.[24-27] The HADS

Depression score will be analyzed as a secondary outcome. As an additional secondary outcome measure we will determine the no-show rate for the initial consultation among each group. We will enter all data into Research Electronic Data Capture (REDCap), a secure, web-based application designed to support data capture for research studies,[28] and export the data into Stata/SE 16.1 for Mac, StataCorp LP (College Station, TX, USA) for analysis.

Statistical analysis

For descriptive statistics we will report categorical data as proportions with 95% confidence intervals and continuous data as means with standard deviations or medians with interquartile ranges as appropriate. As part of the CONSORT diagram[18] we will report the proportion of patients who do not attend their initial cancer consultation, as well as the proportion of patients who attend their initial consultation, but decline to participate in the study, stratified by video group allocation. We will test if the enhanced compassion video reduced the no-show rate to the initial consultation, as well as increased participation in research using the Fisher exact test. We will use Cronbach's alpha to separately test the internal reliability of the HADS anxiety scale, HADS depression scale, and the 5-item compassion measure among our cohort. We will test if the enhanced compassion video group perceived the video oncologist as more (or less) compassionate, as measured by the 5-item compassion measure, than the standard introduction video group using the Wilcoxon rank-sum test.

For the primary outcome, we will use the Wilcoxon rank-sum test to test for a difference in the HADS anxiety scale between the two video groups. We will also perform a sensitivity analysis dichotomizing the HADS anxiety scale into low (< 8) and moderate/high (≥ 8). A cut point of 8 on the HADS subscales has been defined as the optimal cut point for diagnosis screening and is commonly used to define clinically significant symptoms in research studies.[25,29] We will use the Fisher exact test, to test if the proportion of patients with clinically significant symptoms differed

between the two video groups. For our secondary outcome measure we will repeat the same analyses described above using the HADS depression scale in place of the HADS anxiety scale. We will perform the above analyses using intention to treat methodology. The analyses will be repeated in a per protocol fashion excluding patients who state they did not watch the video prior to presentation to the cancer center.

To test if the relationship between video group and anxiety severity differs among pre-specified subgroups we will perform separate multivariable linear regression models with the HADS anxiety scale as the dependent variable, and entering the following patient characteristic along with an interaction term between video group and the characteristic as independent variables: (1) age (decile), (2) sex (male vs. female), (3) race (white vs. non-white), (4) ethnicity (Hispanic vs. non-Hispanic), (5) suspected primary cancer (breast vs. gastrointestinal vs. pulmonary vs. skin vs. central nervous system vs. gynecologic vs. other).

Sample Size calculation

Assuming an alpha of 0.05, power of 0.8, and a standard deviation of 5 for the HADS anxiety scale, based on previous literature,[24,26] in order to detect a clinical meaningful difference (previously defined as a 1.5-point difference)[30] between subjects who viewed the standard introduction video compared to subjects who viewed the enhanced compassion video we will need 176 subjects per group. Assuming a 25% lost to follow-up (i.e. non-attendance to consultation or decline to participate), to ensure accrual of the total sample size of 352, we plan to enroll 470 total subjects.

Discussion

This study aims to test if viewing compassionate statements from an oncologist prior to an initial oncology consultation will reduce the degree of anxiety among patients referred to a cancer center. By randomizing subjects to one of two introduction videos, which differ only in regard to additional compassionate statements, we will be able to test if the compassionate statements themselves have an effect on patient anxiety.

Given anxiety has been shown to decrease the ability to concentrate,[5] decreasing patient anxiety prior to their initial consultation may improve engagement with their healthcare providers and empower them to ask questions about what tests and procedures are most appropriate for them. Such improvement in the clinician-patient interaction may also result in improved clinical assessment, accurate diagnosis, as well as better counseling, therapeutic instruction, and cost-effectiveness.[10] This study is the first step in testing if pre-consultation compassionate statements decrease patient anxiety. If our hypothesis is correct, future research will be warranted to test the effect of pre-consultation compassionate statements on other clinical outcomes such as patient retainment of clinical instructions, medication compliance, and cost-effectiveness. Similarly, a null study will support further research into the timing, delivery mechanism, and “dose” of compassion that may be required to reduce patient anxiety prior to their study visit. Regardless of our results, qualitative research is also warranted to identify other potential intervention targets to strengthen the clinician-patient relationship.

In order to view the videos prior to the initial oncology consultation patients must have an active email account. Thus, subjects without an email account will be excluding potentially limiting generalizability of our results. However, this study will be a first step in determining if clinician compassion can be conveyed to patients prior to their initial oncology consultation and if per-consultation compassion can improve patient outcomes.

Protocol amendments

Any amendments to this protocol will be described along with the rationale and date the change was implemented.

Patient and Public Involvement

We designed this study given previous research has demonstrated that compassionate patient care is considered one of the most important aspects of high quality healthcare by patients and patient family members.[8,31] However, individual patients were not involved in the design of this study.

Data sharing

After review and approval by our study data use committee, we will allow other researchers who submit to us a suitable protocol to have access to the complete de-identified datasets used and/or analyzed during the study, in comma separated value format together with a data dictionary.

Ethics and dissemination

As stated above this study was approved by the Cooper University Health Care Institutional Review Board with alteration of the requirements of obtaining informed consent under 45 CFR 46.116(d). The results from this randomized control trial will be submitted for publication to peer-reviewed journals, and to national meetings in presentation form.

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Author's contributions

All authors have made substantial contributions to this report and have satisfied International Committee of Medical Journal Editors (ICMJE) criteria for authorship. BWR supervised all aspects of the study design and takes responsibility for the paper as a whole. BWR, CCW, AM, GG, and ST contributed to the study design, and development of the video scripts. BWR provided statistical expertise. BWR, CCW, and ST drafted the manuscript. AM and GG read and contributed substantially to revision of the final manuscript. BWR, CCW, AM, GG, and ST approved the manuscript in its final form.

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Competing interest statement

Drs. Trzeciak and Mazzarelli are co-authors of a book on compassion science entitled "Compassionomics". None of the other authors have disclosures.

Cooper University Hospital

INFORMED CONSENT AND HIPAA AUTHORIZATION
TO PERMIT THE USE AND DISCLOSURE
OF PROTECTED HEALTH INFORMATION (PHI)
FOR RESEARCH PURPOSES

TITLE OF STUDY: A pre-consultation compassion video to reduce anxiety among patients referred to a cancer center.

PRINCIPAL INVESTIGATOR: Brian W. Roberts, MD, MSc

DEPARTMENT(S): Department of Emergency Medicine, Department of Medicine, Department of Medicine - Hematology/Oncology

PHONE NUMBER(S): 856-342-2352

SPONSOR: Cooper Health System

What does the research study involve?
You are being invited to take part in a research study. This form is part of an informed consent process. It will give you information to help you decide if you want to volunteer for this research study. Volunteer means you choose to take part. You do not have to take part in this study to receive treatment at Cooper Hospital. The study doctor or his staff will discuss with you what is involved in this research study. If you decide to take part, you and the study doctor or a member of the study team will sign this consent form. You will receive a copy of this consent form to keep. If you have questions at any time during the research study, you should feel free to call any of the doctors listed above and ask your questions until you receive answers that satisfy you.

What is the purpose of this research study?
Patients coming to a cancer center for the first time may have a lot of anxiety. You are being asked to participate in this study because you are here for your first appointment at MD Anderson at Cooper. The purpose of this study is to see if patients who are coming to the cancer center for the first time are anxious.

If you decide to take part in this study, you will be asked to complete a survey. The survey asks questions about anxiety and depression that you may be feeling. Prior to your visit today you were sent a link to view one of two videos. Both videos are very similar. Which video you were sent was determined at random (like flipping a coin). Both videos go over your care here at MD Anderson at Cooper.

The survey also asks questions about your thoughts of the video you were sent. It is ok if you did not watch the video. You can skip the questions about the video if you did not watch it. This survey is not part of routine care. We expect it will take about 5-10 minutes to complete the survey. Being part of this study will in no way affect the care you receive for your medical needs.

We will record the following information that would be collected from you anyway as part of usual care (i.e. the measurements are not being done for research):

- We will record information about your past medical history, demographics, and details of you visit today.

What risks are there?
This study will not change the care you receive. We do not anticipate any medical risks from being in this study. You do not need to answer any questions you feel uncomfortable with.

There is a risk of a loss of confidentiality of your information recorded for research. We will record information on password protected forms, which are stored on a secure server. This will reduce the risk of loss of your information. A study number will be used on these forms. We will not use your name. The only link between your data and your name will be kept on a password protected computer server here at Cooper. Once the data collection for all subjects is complete, data that could identify you will be deleted. At the completion of this study the data collected will be shared publically so other researchers may analyze the data. However, this shared data will not contain any identifying information. It will not be able to be linked back to you (NO individual will be personally identified).

What benefits are there?
You may have a direct benefit because the survey asks questions about anxiety and depression. This may uncover symptoms that may not be found at this time if you were not in the study. If these symptoms are uncovered, it is possible that they are having a negative impact on your life. Your cancer doctor should know about them. The results of this survey will be shared with your cancer doctor.

Also, the results of this study may help future patients with cancer.

What are your alternatives (other choices) if you do not take part in this study?
Your alternative is to choose not to be a part of this study. You will receive standard care for your condition whether or not you participate in this study.

When can your participation be terminated by the investigator?
The investigator may terminate your participation in the study if you are not able to complete the required survey.

Are there any other costs?
There are no costs to you for participating in this study.

Will you be paid for participation?
You will not be paid for participating in this study.

What will happen if you withdraw?
Tell the investigator if you want to withdraw from the study. If you withdraw from the study, you will continue to have access to health care at the Cooper Health System.

Will you be told about new information that might affect your decision to take part in this research?
During the study, you will be told if any new information is learned that could affect your willingness to stay in the study.

USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION (PHI) FOR RESEARCH PURPOSES

Will your information be kept confidential?

The privacy regulations of a law passed by Congress became effective on April 14, 2003. The law is called the Health Insurance Portability and Accountability Act, HIPAA for short. The law gives subjects in research studies certain rights about their protected health information. Protected health information (PHI) is information about a person's physical or mental health that can be identified with or linked to that particular person. If you sign this form you are giving the investigators, their staff, and certain other people described in this form your permission to use your protected health information for this research study.

The information collected about you for this study is called "protected health information" (PHI). It includes: demographic information (e.g., your name, medical record), medical history, and your answers to the study survey.

All of this information is being collected because you are participating in this research study.

Information about you will also be collected from your medical records that are located in Cooper University Hospital's electronic medical records. The information that is collected will be used to decide if you qualify to participate in this research, to follow your treatment, and will be analyzed to answer the research questions.

To help maintain the confidentiality of your study records, you will be assigned a subject number. All of your study related-information will have only your subject number. Identifying information, like your name and medical record number, will be linked to your subject number but will be kept separate from your study-related information. Your study documents will be stored on a secure password-protected computer server. The information from this study may be published in scientific journals or presented at scientific meetings but you will not be personally identified in these publications and presentations.

By signing this form, you are allowing the following people or groups to have access to the information described above (your PHI).

The research team, which includes the investigators listed on this form and other personnel involved in this specific study need to analyze the data.

Cooper's Institutional Review Board (IRB), a committee that reviews, approves, and monitors research involving human subjects may look at your study records.

All of these people and entities are obligated to protect your PHI.

You have the right to limit the use and sharing of your PHI, and you have the right to see your research study records and know who else is seeing them. You will not be allowed to see your health information that is created or collected during the course of the research. After the research is finished, however, you may see this information.

You are authorizing us to use and disclose your PHI until the end of the research study. You may revoke this authorization to use and share your PHI at any time by contacting the principal investigator, in writing, at the address on the front of this form. If you decide not to authorize the investigator to use and disclose your PHI or you revoke this authorization, you will no longer be

able to participate in this research study, and the use or sharing of future PHI will be stopped. However, the PHI that has already been collected may still be used.

Whom can you contact if you have a question?
If you have any questions about this research, you can contact the principal investigator at the number on the first page.

You should call the Chief Medical Officer or his representative at (856-342-3071) (a) if you have any questions about your rights as a research subject or your rights related to the research use of your PHI, (b) if you believe that you have not been told about all the risks, benefits, and alternative treatments, (c) if you believe that you are being forced to stay in this study when you do not want to, or (d) you have any complaints about the research.

You should also contact that person if you believe that you have not been adequately informed as to the risks, benefits, or alternative procedures of this research study, or that you are being pressured to participate in the study against your wishes.

If you have any questions about the research or your rights as a subject or any complaints about the research, you may also contact the Institutional Review Board (IRB) of the Cooper Health System. The IRB is responsible for protection of subjects participating in this research project. The address of the IRB is E&R Building, 401 Haddon Ave., Room 288, Camden, NJ 08103. The phone number is 856 757-7832.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. At the conclusion of the study, the web site may include a summary of the results. However, this web site will not include information that can identify you. You can reach this web site at any time.

CONSENT STATEMENT

Your participation and your decision to allow the use of your PHI are entirely voluntary. You do not have to participate or let us use your PHI. If you decide not to participate or not to let us use your PHI or you decide to stop participating or to stop letting us use your PHI, it will not affect your treatment at Cooper University Hospital. Your doctors will continue to treat you the way they always have.

All of the above has been explained to me. All of my questions have been answered. I can ask questions that I have about the research or about the use and disclosure of my PHI at any time. My questions will be answered by one of the investigators listed on the first page of this form.

By signing this form I agree to participate in this study and I agree to the use and disclosure of my PHI for the purposes described above. A copy of this form will be given to me.

Signature Block for Adult Subjects

Printed Name of Subject : _____

Signature: _____ Date:_____ Time: _____

I have discussed the study described above with the subject.

Printed Name of Person Obtaining Consent: _____

Signature: _____ Date:_____ Time: _____

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____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	____Page 1_____
Funding	4	Sources and types of financial, material, and other support	_Page 16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Pages 1 and 16
	5b	Name and contact information for the trial sponsor	__N/A___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_N/A___
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_N/A_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 4
	6b	Explanation for choice of comparators	Page 4
Objectives	7	Specific objectives or hypotheses	Page 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 6
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 6
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 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Pages 7-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	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	Pages 9-10
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)	Pages 6-7

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 11_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Pages 6-7_____
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 7_____
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 7_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_Page 7_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 7_____
	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	Pages 9-10_____
	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	Pages 9-10_____

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 10_____
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	Pages 10-11___
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_Pages 10-11__
	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)	Page 11_____
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	N/A_____
	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	N/A_____
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	N/A_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_Page 6_____
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 11_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 16
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 12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 12
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplemental
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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