BMJ Open

Protocol for the ORaCIES study: an Online Randomised controlled trial to improve Clinical Estimates of Survival using a training resource for medical students

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-025265
Article Type:	Protocol
Date Submitted by the Author:	06-Jul-2018
Complete List of Authors:	Oostendorp, Linda; University College London, Marie Curie Palliative Care Research Department White, Nicola; University College London, Marie Curie Palliative Care Research Department Harries, Priscilla; Brunel University London, Clinical Sciences Yardley, Sarah; University College London, Marie Curie Palliative Care Research Department; Central and North West London NHS Foundation Trust Tomlinson, Christopher; Imperial College London, Bioinformatics Data Science Group; University College London, Marie Curie Palliative Care Research Department Ricciardi, Federico; University College London, Marie Curie Palliative Care Research Department Gokalp, Hulya; Brunel University Department of Clinical Sciences; Ondokuz Mayis Universitesi, Department of Electrical and Electronic Engineering Stone, Patrick; University College London, Marie Curie Palliative Care Research Department
Keywords:	Prognosis, End of Life, PALLIATIVE CARE, online training resource, medical students, randomised controlled trial

Study protocol

Protocol for the ORaClES study: an Online Randomised controlled trial to improve Clinical Estimates of Survival using a training resource for medical students

Linda JM Oostendorp,[1*] Nicola White,[1*] Priscilla Harries,[2] Sarah Yardley,[1,3] Christopher Tomlinson,[1,4] Federico Ricciardi,[1] Hülya Gökalp,[2,5] Patrick Stone[1]

* These authors contributed equally to this work

[1] UCL, Marie Curie Palliative Care Research Department, Division of Psychiatry, University College London, London, United Kingdom;

[2] Brunel University London, Department of Clinical Sciences, London, United Kingdom;

[3] Central and North West London NHS Foundation Trust, London, United Kingdom;

[4] Imperial College London, Department of Surgery & Cancer, London, United Kingdom;

[5] Ondokuz Mayis University, Department of Electrical and Electronic Engineering, Samsun, Turkey.

Correspondence to: Dr Linda Oostendorp: l.oostendorp@ucl.ac.uk

ABSTRACT

Introduction: Clinicians often struggle to recognise when palliative care patients are imminently dying (last 72 hours of life). A previous study identified the factors that expert palliative care doctors (with demonstrated prognostic skills) had used to form a judgement about which patients were imminently dying. This protocol describes a study to evaluate whether an online training resource showing how experts weighted the importance of various symptoms and signs can teach medical students to formulate survival estimates for palliative care patients that are more similar to the experts' estimates.

Methods and analysis: This online double-blind randomised controlled trial will recruit at least 128 students in the penultimate or final year of medical school in the UK. Participants are asked to review three series of vignettes describing patients referred to palliative care and provide an estimate about the probability (0-100%) that each patient will die within 72 hours. After the first series, students randomised to the intervention arm are given access to an online training resource. All participants are asked to complete a second series of vignettes. After two weeks, all participants are asked to complete a third series. The primary outcome will be the probability of death estimates (0-100%) provided by students in the intervention and control arms for the second series of vignettes. Secondary outcomes include the maintenance effect at two week follow-up, weighting of individual symptoms and signs, and level of expertise (discrimination and consistency).

Ethics and dissemination: Approval has been obtained from the UCL Research Ethics Committee (8675/002) and local approvals will be obtained as appropriate. Results will be published in peer-reviewed journals using an open access format and presented at academic conferences. We will also publicise our findings on the Marie Curie website.

Trial registration number: Clinical Trials.gov NCT03360812; pre-results

Keywords (3-6): Prognosis, End of Life, Palliative care, online training resource, medical students, randomised controlled trial

Strengths and limitations of this study

- This is an evaluation of a novel training resource for improving prognostic skills in recognising palliative care patients who are imminently dying.
- A multicentre randomised controlled trial design has been used, with (partial) blinding of participants and researchers and including a follow-up to test for any maintenance effects.
- This study will provide evidence about whether an online training resource can influence how medical students make prognostic decisions in an experimental setting, using a prognostic task that may lack some ecological validity since it relies on an online rather than a face-to-face assessment of palliative care patients. Therefore, further testing of the intervention in routine medical education and assessment of the accuracy of clinicians' performance in real-world prognostic tasks will be required.

INTRODUCTION

When living with an incurable disease that shortens life expectancy, many patients and their relatives wish to receive information on what the future might bring, including a time frame of the expected length of survival.[1 2] Several reports on care near the end of life have highlighted that recognition of the dying phase in palliative care patients is inaccurate, and that this can have a significant negative impact on patient care at the end of life.[3-5] Being aware that death is imminent can help patients, families, and professionals to engage in discussions about goals of care and make decisions about appropriate care and treatment, including hospice admission and starting end-of-life care plans.[6 7] In addition, better prognostic awareness can shift patients' preferences from aggressive life-prolonging treatments towards comfort-oriented care.[7-10] It can also help patients and families to make plans for the time remaining, and discuss practical issues such as estate management and funeral planning.[7] For families, information about imminent death can help to make decisions about how to look after their loved one, for example deciding whether the patient can remain at home or deciding whether to stay overnight or invite other relatives to visit.[7]

While some prognostic models are available, in daily clinical practice it is usually the responsibility of a clinician to formulate a survival estimate.[11 12] Making accurate survival predictions is notoriously difficult, estimates are often overoptimistic and prognostic skills do not necessarily develop over time.[13-15] Many doctors try to avoid prognostication and feel insufficiently prepared to perform this clinical task.[16] The European Association for Palliative Care (EAPC) has recommended that training could improve the accuracy of clinicians' survival estimates, but there was little evidence to support this recommendation.[17] Virtually no education or training resources are available to specifically improve prognostic skills and a better understanding of how clinicians formulate their predictions is crucial to develop such resources.

This study will describe and evaluate an intervention for predicting imminent death (i.e. death within 72 hours). Given the current lack of training resources to improve prognostic

performance, this study will, as a proof of principle, focus on medical students who have limited clinical experience so that any effects of the intervention are more likely to be detected.

The intervention

The development of the training resource was informed by Social Judgement Theory, which assumes that judgements (prognostic decisions) result from the integration of different types of information, known as "cues".[18] Judgement analysis attempts to capture an expert's "judgement policy" using a multiple regression procedure to calculate the relative weights that the experts attach to different cues. In a previous study, we have used judgement analysis[19] to identify the clinical cues (e.g. breathing pattern and the presence of respiratory secretions) that expert clinicians use to formulate a prognosis of imminent death.[20] The training resource will provide students with task information on how to use the most important cues when making prognostic decisions. Outside of the palliative care context this approach has been used successfully to train a variety of other student populations about how to make decisions more aligned to those of experts.[21-24]

Experts can be identified in several ways.[25] In our previous study, expert palliative care doctors were selected based on the validity of their judgements.[26] Palliative care doctors were asked to complete an online prognostic test consisting of a series of vignettes based on real cases and their prognostic estimates were compared against actual survival. The top 20% of performers were defined as 'experts' and were invited to complete a second series of fictional vignettes. We will evaluate students' prognostic performance by comparing students' estimates against the estimates provided by the experts for the same series of fictional vignettes. In addition, to gain a fuller picture of the expertise as demonstrated by the students, we will assess the extent to which they are able to discriminate between patients with different severities of symptoms/signs and to consistently make similar prognostic decisions for patients with similar symptoms/signs.[25] It is important to note however that high levels of discrimination and consistency do not guarantee accuracy,[27] therefore

these results will be evaluated in conjunction with the comparison of students' estimates against the experts' estimates.

The training resource will be offered to study participants in an online format, which will enable easy access at the students' convenience, regardless of geographical location.[28-30] If the training material is found to be successful, the online format will enable widespread dissemination and facilitate easy updating and students will be able to re-access the information as and when required.[28 31] Studies have indicated that e-learning in medical education, as a supplement to traditional ways of teaching, is perceived as acceptable and evaluated as useful by students.[31 32]

Objectives

The aim of this trial is to evaluate whether an online training resource can teach medical students to model the prognostic decisions of expert palliative care doctors about which palliative care patients are likely to die within 72 hours. This study will:

- Assess if the probability of death estimates formulated by medical students become more similar to experts' estimates after completing an online training resource (primary objective);
- Determine if any effect of the online training resource is maintained after two weeks;
- Evaluate if the online training resource changes the weighting of individual symptoms/signs, and whether the students' judgement policies become more similar to the experts' judgement policies.
- Assess if the online training resource improves the expertise of the medical students, in terms of the ability to discriminate between patients and be consistent in decisions.

Trial design

This is an online multicentre double-blind randomised controlled trial involving an intervention arm that will receive an online training resource for prognostication and a control arm. Medical students will be randomised to these two parallel arms using a 1:1 allocation ratio. Since this will be the first

trial of an intervention to improve prognostic skills, the study is designed as a proof of principle study, evaluating whether the training resource can influence how medical students make prognostic decisions in an experimental setting.

METHODS AND ANALYSIS

This protocol follows guidance from the SPIRIT 2013 statement,[33] and the completed SPIRIT checklist is available as an online supplementary file.

Study setting

This study will be conducted online using a purpose-built study website hosted by UCL. The study will recruit students from up to 33 medical schools in the United Kingdom, approved by the Medical Schools Council.[34] As we are offering a financial incentive for participating, it is important to control the potential total number of participants. We will approach individual medical schools as needed until the sample size has been achieved.

Eligibility criteria

Eligible participants should (1) be over 18 years of age; (2) be enrolled on a registered medical course within the UK; (3) be in the penultimate or final year of the course; (4) have sufficient English language proficiency; and (5) be willing and able to provide consent as indicated by taking part in the online study assessments. Students in the penultimate and final year are felt to have sufficient knowledge to understand the terminology in the vignettes and will have had at least one year of clinical experience as part of their training. Recruitment strategies will be targeted at students in the penultimate and final year of participating medical schools to minimise the risk of non-eligible students taking part. Participants will be asked to confirm their eligibility.

Intervention

The intervention is a newly developed online training resource to improve the recognition of imminent death in palliative care patients. The content was based on a previous study in which we used judgement analysis[19] to identify the clinical cues that expert palliative care doctors use to formulate a prognosis of imminent death in terminally ill inpatients.[20] Experts were presented with

50 vignettes describing hypothetical palliative care patients (see Figure 1 for a sample vignette). There were seven symptoms and signs ('cues') available in each vignette: (1) Palliative Performance Scale (PPS) score[35]; (2) Richmond-Agitation Sedation Scale (RASS)score[36]; (3) rate of decline in general condition; (4) breathing pattern; (5) respiratory secretions; (6) urine output; and (7) peripheral cyanosis. The first four cues were the most heavily weighted in the decision making process of the experts.[26]

Study participants will be presented with the same vignettes and cues that had been presented to the expert palliative care doctors in the previous study. The online training resource will educate the participants on how to use the cue information when formulating a prognosis of imminent death, providing a description of the four most important cues and, where possible, graphical information for ease of understanding. The intervention will be implemented via the study website and should take approximately 15 minutes to complete.

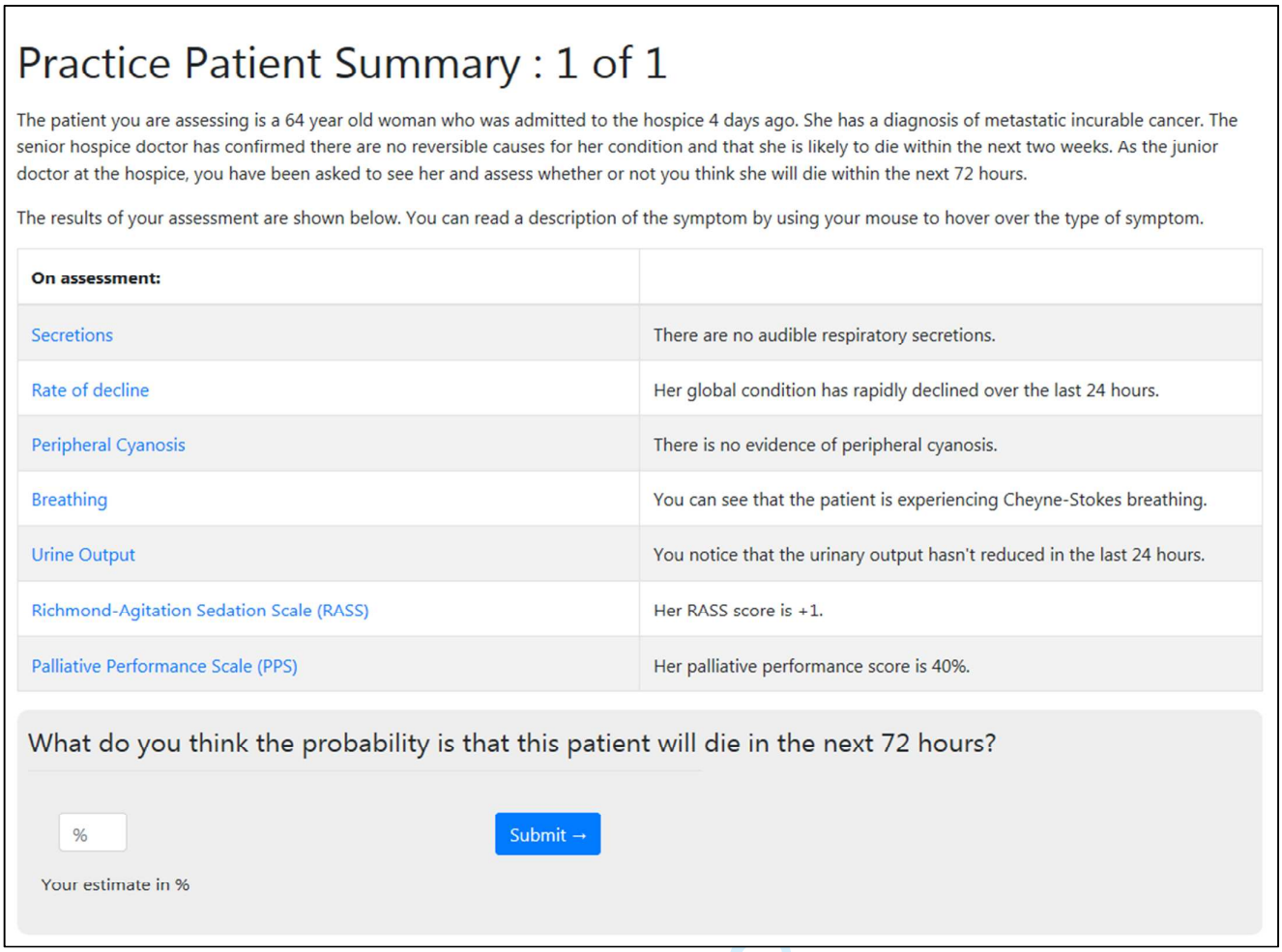
Data collection procedure and outcomes

The data collection procedure is shown in the study flow diagram in Figure 2. After obtaining informed consent, participants will be asked a number of questions to obtain a description of the sample and enable subgroup analyses. This includes demographic questions (age, gender, ethnicity), course detail (place of study, year of study), and palliative care experience (training, placements, experience, confidence). Participants are asked for their name and university email address (to be entered twice for validation). This will allow them to log out and return to the same place at a more convenient time, which is hoped to reduce attrition. It will also allow the research team to check whether participants are affiliated with the universities the study is recruiting from, to populate the certificate of participation, and to send out reminders and gift vouchers.

Participants will then be randomised to either the intervention arm or control arm. Next, participants are given instructions, and are reminded to complete the study individually, in a quiet

location, free from distraction at a time and place of their choosing. Following this, they will be able to complete a practice vignette to familiarise themselves with the online environment.

All participants will then be asked to review a first series of 40 vignettes. Each vignette will present a description of a patient (the stem), which is identical for each vignette, with seven cues that describe differing severities of symptoms or signs that vary between vignettes (see Figure 1). Participants will be asked to provide a percentage estimate of the probability that the patient will die within 72 hours (0% means no chance of death and 100% means certain death). This series of 40 vignettes includes 30 vignettes presented in random order for each participant, followed by 10 repeated vignettes, also in random order. These repeated vignettes are included to assess participants' level of expertise, as measured by the discrimination and consistency of probability of death estimates.[37] The order in which the seven cues are presented are also randomised per participant, to prevent order effects.



Practice Patient Summary : 1 of 1

The patient you are assessing is a 64 year old woman who was admitted to the hospice 4 days ago. She has a diagnosis of metastatic incurable cancer. The senior hospice doctor has confirmed there are no reversible causes for her condition and that she is likely to die within the next two weeks. As the junior doctor at the hospice, you have been asked to see her and assess whether or not you think she will die within the next 72 hours.

The results of your assessment are shown below. You can read a description of the symptom by using your mouse to hover over the type of symptom.

On assessment:	
Secretions	There are no audible respiratory secretions.
Rate of decline	Her global condition has rapidly declined over the last 24 hours.
Peripheral Cyanosis	There is no evidence of peripheral cyanosis.
Breathing	You can see that the patient is experiencing Cheyne-Stokes breathing.
Urine Output	You notice that the urinary output hasn't reduced in the last 24 hours.
Richmond-Agitation Sedation Scale (RASS)	Her RASS score is +1.
Palliative Performance Scale (PPS)	Her palliative performance score is 40%.

What do you think the probability is that this patient will die in the next 72 hours?

% Submit →

Your estimate in %

Figure 1 Sample vignette

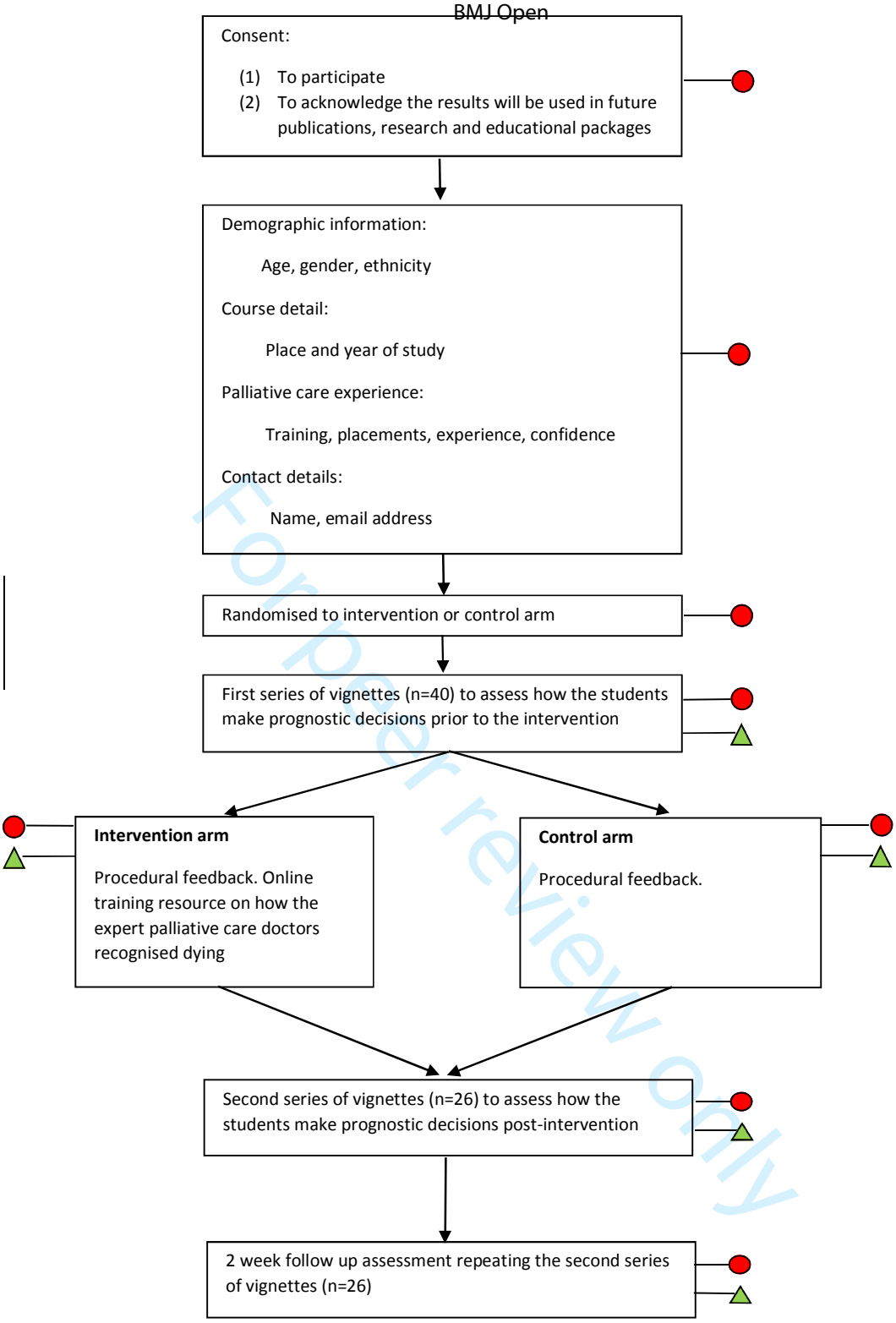


Figure 2 Study flow diagram

Participants in the intervention arm will then receive the online training resource, while participants assigned to the control group will not receive this additional information but will be informed that they are approximately half way through the study. All participants will be asked to provide probability of death estimates for a further series of 26 vignettes (including six repeated vignettes), in the same format as the first series of vignettes. The participants in the intervention arm will be able to access the online training resource during this second series of vignettes should they wish to do so. It is estimated that it will take up to 45 minutes to complete the first and second series of vignettes.

Two weeks after completing the second series of vignettes, participants will be asked to repeat the second series of 26 vignettes, although they will not be informed that the cases are the same as those that they have previously completed. Again, the vignettes will be presented in random order to minimise the risk of participants remembering vignettes or the estimates they provided previously. Participants in the intervention arm will not be given access to the online training resource on this occasion. This will enable us to determine if the effect of the intervention has lasted over time. It is estimated that this assessment will take up to 15 minutes to complete.

All participants can log out from the study website and return at a later time, at any point through the trial. Participants will be sent a reminder email when the third series of vignettes is due and if they start but do not finish the study. Participants will have a four week time window to complete the first and second series of vignettes, and another four week time window to complete the third series of vignettes. The web-based system will track the time students spend on completing the vignettes and the online training resource, if applicable. To improve data quality, drop-down lists are used where possible and participants will not be able to move on to the next page if essential information is missing or if information has been entered in an incorrect format. The online environment will be piloted by the study team.

Primary outcome

The primary outcome will be the continuous probability of death estimates (0-100%) provided from the students for the second series of vignettes.

Secondary outcomes

a. The maintenance effect will be measured by using the probability of death estimates as described for the primary outcome measure at the two week follow-up time point.
b. Cue weighting of the individual students will be compared against that of the experts. When students provide a probability of death estimate they weigh information or "cues" from the vignette as part of the process. By asking students to make a number of decisions on a series of vignettes in which cue values are varied, it is possible to model the weights assigned to the various cues.
c. The level of expertise will be assessed with the Cochran-Weiss-Shanteau (CWS) index of expertise.[25] The CWS index captures the degree of expertise demonstrated in a set of responses and consists of the ratio of discrimination to inconsistency.[37] This will help us to understand if the participants become better at discriminating between patients after the intervention, and if their prognostic decisions become more consistent.

Sample size

A sample of 128 subjects (64 subjects in each group) is required to detect a medium effect size (Cohen's d = 0.5) between the intervention and control groups, assuming a common standard deviation, 80% power and using a two sample t-test at the 5% significance level. A medium effect size of 0.5 is described as an effect that is likely to be visible.[38] Larger effect sizes were achieved in previous evaluation studies of similar online training resources by one of the members of our study team (PH).[22-24] We estimate that it will be necessary to recruit approximately 183 subjects in order to obtain a final sample size of 128 participants with complete data sets for analysis. The anticipated

30% drop-out rate (i.e. participants who start but do not complete the task) has been estimated on the basis of previous similar studies by our own group. Recruitment will start from April 2018 and we anticipate to complete recruitment by the end of December 2018.

Recruitment

Recruitment strategies will differ slightly between medical schools to comply with local ethical/governance requirements. These methods may include: 1) The palliative care lead at each participating medical school introducing the study to students; 2) The course leader or administrator at each participating medical school distributing an email to all penultimate and final year students; and (3) Advertising the study using newsletters, virtual notice boards and student associations. The study recruitment materials will show the link to the study website and the study email address for students to contact the study team.

Randomisation and blinding procedures

Participant randomisation will be undertaken automatically through the web-based system using a pre-generated randomisation list with a block size of 10. This list will be generated by a member of the study team who will not be involved in recruitment (CT), using computer-generated random numbers.

Researchers and participants will be blinded as far as possible. For data monitoring purposes, researchers will be able to check how many participants are randomised to each arm, but will be blinded to which arm will be the intervention arm. All other data that could reveal the allocation (e.g. time taken to complete the intervention) will be concealed from the researchers who will be monitoring the data (NW and LO) and the statistician who will conduct the analysis (FR). The allocation will remain concealed until the statistician has completed the analysis. Participants will be partially blinded to the nature of the intervention and the randomised controlled design of the study to minimise attrition in the control group. Rather than telling participants that half will receive the

intervention and half will not, we will inform students that they will receive an online training resource in one of two different formats.

Inducements for participation

As a gesture for the time taken to complete the study and to promote participant retention, participants will be offered a total of £30 gift vouchers for completing the study. Participants will be offered a £10 gift voucher for completing the first stage of the study and a £20 gift voucher for completing the two week follow-up. The study will be open for new participants until 64 complete cases are available in each group. When recruitment closes, students who have started the study will be able to complete the remaining assessments and will be eligible to receive the vouchers. Participants who complete the research will receive a certificate of completion that will add towards their academic portfolio. Taking part in the study will give each participant an opportunity to develop some of the clinical skills required to recognise dying palliative care patients. If the resource is found to be effective, then this could benefit future medical students and palliative care patients.

Public engagement

We invited two fourth-year medical students to review the recruitment documents and pilot the website. Both students provided valuable comments, resulting in several changes in the recruitment email, advertisement material, and participant information sheet. These changes mainly involved emphasising certain aspects of the study to make it more appealing to medical students.

Statistical methods

Demographic characteristics, course detail and palliative care experience will be summarized by treatment assigned and overall. As a result of the randomisation process, we expect the groups to be balanced. Categorical data will be presented as numbers and percentages. Continuous data will either be described with mean and standard deviation, or median and interquartile range, pending

the distribution. We will produce a CONSORT flow diagram of all participants (http://www.consort-statement.org/).

In this proof of principle study, we are seeking to evaluate whether an online training resource can influence how medical students make prognostic decisions in an experimental setting. Therefore, we will employ a per-protocol analysis where those participants who do not complete all vignettes or violate the protocol (e.g. putting the same answer for every vignette) will be removed from the analysis. To assess if the online training resource affected the probability of death estimates provided, we will calculate the degree of agreement between the study participants' probability of death estimates for the first and second series of vignettes and the probability of death estimates obtained from the experts in our previous study. Suitable regression models will be fitted to estimate the effect of the intervention, comparing agreement with the experts for those who received it and those who did not. In addition to this, we will also visualise the degree of agreement in both groups for the first and seconds series of vignettes, using the Bland Altman method.[39]

The maintenance of the study effect will be measured by repeating the primary outcome analysis with the estimates from the two week follow-up time point. To assess whether the intervention altered the judgement policy of the participants, we will examine participants' cue weights for the three series of vignettes and correlate them with the expert's cue weights presented in the training information. The CWS performance index and the subcomponents discrimination and consistency will be compared between the intervention and control arms for the three series of vignettes.[25 37]

Data monitoring and adverse events

Throughout the trial, the research team will review recruitment figures. Researchers will check the responses given by the participants, and the time taken by each participant to complete the vignettes, to assess for compliance with the protocol. Participants may be excluded from the analysis

if their response record strongly suggests that they did not comply with the study protocol (e.g. all items answered with the same response or too speedily). The Trial Management Group (PS, PH, LO, NW, CT, SY, FR, HG) will be responsible for overseeing the trial and will meet regularly (at least four times per year) to review recruitment figures.

This is a very low risk study. There are no expected side effects of our intervention and this study will not have a Data Monitoring Committee.

ETHICS AND DISSEMINATION

Approval has been obtained from the UCL Research Ethics Committee (8675/002) and local approvals will be obtained as appropriate. In case any protocol amendments are required, these will be reviewed by the Trial Management Group before submission to the relevant committees, and the trial registry will be informed where necessary.

Consent

Participants will be given a brief summary of what the study involves in the recruitment email. On the website, there will be a welcome page with information about the study and the Participant Information Sheet is available to download. However, as described above, participants will be partially blinded to the nature of the intervention and the randomised controlled design of the study. The participants will be reminded that they are free to withdraw at any time. Informed consent will be obtained via two checkboxes before starting the study assessments: (1) to participate; and (2) to acknowledge the results will be used in future publications, research and educational packages. Those who do not consent will not be able to continue to the next page.

On completion of the second and third series of vignettes, a debrief page will be shown to remind the participant what the results will be used for. The contact details for the study team will also be displayed should they have any concerns or issues they wish to follow-up. This debrief will not include any more detailed explanation of the two groups students were randomised to or the active intervention, as we feel this would not be appropriate. Students will participate at a time convenient to them, and we would not want students who have completed the study to disclose this information to others who have yet to participate.

Data management

Our study received ethics approval before the introduction of the GDPR on 25th May 2018. The documents that were approved state that all data will be handled in accordance with the UK Data

Protection Act 1998. No formal amendment was required following the introduction of the GDPR, but we added a transparency message to the study website to make participants aware of how we will use their information. Participants will be asked for their names and university email address as a personal identifier as well as being assigned a unique participant ID. During the trial, all data will be kept securely on a web-based database, which is encrypted and password protected. The database will be accessible to approved members of the research team only as access to the intranet will be restricted to their IP addresses only. Recruitment strategies may include the study being introduced to students by their local palliative care lead. This person will not have access to the study database and will therefore not be aware which students participated and which did not, nor will he or she have access to the prognostic performance data of individual students.

Once all data have been reviewed and the gift vouchers have been distributed, the names and email addresses will be deleted from the web-based database in a secure manner and only the participant ID will be referenced. The final trial database will be downloaded from the website by the research team for statistical analysis and UCL will act as the data controller of such data for the study.

Dissemination policy

Study results will be published in peer-reviewed, indexed journals using an open access format, and the results will be presented at academic conferences. Authorship eligibility will be in accordance with The International Committee of Medical Journal Editors. We will also publicise our findings on the Marie Curie website. If the online training resource is proven effective, it will be made freely available after the trial. Data (suitably anonymised) may be shared with other research groups if a reasonable request is submitted to and agreed by the CI.

REFERENCES

1. Parker SM, Clayton JM, Hancock K, et al. A systematic review of prognostic/end-of-life communication with adults in the advanced stages of a life-limiting illness: patient/caregiver preferences for the content, style, and timing of information. *J Pain Symptom Manage* 2007;34(1):81-93. doi: 10.1016/j.jpainsymman.2006.09.035 [published Online First: 2007/05/29]
2. Steinhauser KE, Christakis NA, Clipp EC, et al. Factors considered important at the end of life by patients, family, physicians, and other care providers. *JAMA* 2000;284(19):2476-82. [published Online First: 2000/11/14]
3. Neuberger J. More care, less pathway: a review of the Liverpool Care Pathway. *Department of Health* 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/212450/Liverpool_Care_Pathway.pdf.
4. Parry R, Seymour J, Whittaker B, et al. Rapid evidence review: pathways focused on the dying phase in end of life care and their key components. *Nottingham: University of Nottingham and the NHS End of Life Care Programme* 2013;5
5. Leadership Alliance for the Care of Dying People. One chance to get it right: Improving people's experience of care in the last few days and hours of life. 2014. http://wales.pallcare.info/files/One_chance_to_get_it_right.pdf.
6. Kiely BE, Stockler MR, Tattersall MH. Thinking and talking about life expectancy in incurable cancer. *Semin Oncol* 2011;38(3):380-5. doi: 10.1053/j.seminoncol.2011.03.007 [published Online First: 2011/05/24]
7. Glare PA, Sinclair CT. Palliative medicine review: prognostication. *J Palliat Med* 2008;11(1):84-103. doi: 10.1089/jpm.2008.9992 [published Online First: 2008/03/29]
8. Mack JW, Weeks JC, Wright AA, et al. End-of-life discussions, goal attainment, and distress at the end of life: predictors and outcomes of receipt of care consistent with preferences. *J Clin Oncol* 2010;28(7):1203-8. doi: 10.1200/JCO.2009.25.4672 [published Online First: 2010/02/04]
9. Weeks JC, Cook EF, O'Day SJ, et al. Relationship between cancer patients' predictions of prognosis and their treatment preferences. *JAMA* 1998;279(21):1709-14. [published Online First: 1998/06/12]
10. Wright AA, Zhang B, Ray A, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. *JAMA* 2008;300(14):1665-73. doi: 10.1001/jama.300.14.1665 [published Online First: 2008/10/09]
11. Woelk CJ. How long have I got? *Can Fam Physician* 2009;55(12):1202-06.
12. Tanneberger S, Malavasi I, Mariano P, et al. Planning palliative or terminal care: the dilemma of doctors' prognoses in terminally ill cancer patients. *Ann Oncol* 2002;13(8):1320-2; author reply 22-3. [published Online First: 2002/08/16]
13. Glare P, Sinclair C, Downing M, et al. Predicting survival in patients with advanced disease. *European Journal of Cancer* 2008;44(8):1146-56.
14. White N, Reid F, Harris A, et al. A systematic review of predictions of survival in palliative care: How accurate are clinicians and who are the experts? *PloS one* 2016;11(8):e0161407.
15. Glare P, Virik K, Jones M, et al. A systematic review of physicians' survival predictions in terminally ill cancer patients. *BMJ* 2003;327(7408):195-8. doi: 10.1136/bmj.327.7408.195 [published Online First: 2003/07/26]
16. Christakis NA, Iwashyna TJ. Attitude and self-reported practice regarding prognostication in a national sample of internists. *Arch Intern Med* 1998;158(21):2389-95. [published Online First: 1998/11/25]

17. Maltoni M, Caraceni A, Brunelli C, et al. Prognostic factors in advanced cancer patients: evidence-based clinical recommendations—a study by the Steering Committee of the European Association for Palliative Care. *Journal of Clinical Oncology* 2005;23(25):6240-48.
18. Cooksey RW. The Methodology of Social Judgement Theory. *Thinking & Reasoning* 1996;2(2-3)
19. Cooksey RW. Judgment analysis: Theory, methods, and applications. San Diego, CA, US: Academic Press 1996.
20. How to Identify Doctors who Are Best at Recognising Dying Patients. EAPC 2017 15th World Congress of the European Association for Palliative Care; 2017; Madrid, Spain.
21. Wigton RS, Poses RM, Collins M, et al. Teaching old dogs new tricks: using cognitive feedback to improve physicians' diagnostic judgments on simulated cases. *Academic Medicine* 1990;Sep;65(9 Suppl):S5-6.
22. Harries P, Tomlinson C, Notley E, et al. Effectiveness of a decision-training aid on referral prioritization capacity: a randomized controlled trial. *Medical Decision Making* 2012;32(6):779-91.
23. Harries P, Davies M, Gilhooly K, et al. Educating novice practitioners to detect elder financial abuse: a randomised controlled trial. *BMC medical education* 2014;14(1):21.
24. Harries P, Unsworth C, Gokalp H, et al. A randomised controlled trial to test the effectiveness of decision training on assessors' ability to determine optimal fitness-to-drive recommendations for older or disabled drivers. *BMC Med Educ* 2018;18(1):27. doi: 10.1186/s12909-018-1131-4 [published Online First: 2018/02/15]
25. Weiss DJ, Shanteau J. Empirical assessment of expertise. *Hum Factors* 2003;45(1):104-16. doi: 10.1518/hfes.45.1.104.27233 [published Online First: 2003/08/15]
26. How Is Imminent Death Recognised? A Study to Understand the Decision Making Process of Expert Prognosticators. 10th World Research Congress of the European Association for Palliative Care (EAPC); 2018; Bern, Switzerland.
27. Weiss DJ, Shanteau J, Harries P. People Who Judge People. *J Behav Dec Making* 2006;19:441–54.
28. Choules AP. The use of elearning in medical education: a review of the current situation. *Postgrad Med J* 2007;83(978):212-6. doi: 10.1136/pgmj.2006.054189 [published Online First: 2007/04/04]
29. McKimm J, Jollie C, Cantillon P. ABC of learning and teaching: Web based learning. *BMJ* 2003;326(7394):870-3. doi: 10.1136/bmj.326.7394.870 [published Online First: 2003/04/19]
30. Ellaway R, Masters K. AMEE Guide 32: e-Learning in medical education Part 1: Learning, teaching and assessment. *Med Teach* 2008;30(5):455-73. doi: 10.1080/01421590802108331 [published Online First: 2008/06/26]
31. Ruiz JG, Mintzer MJ, Leipzig RM. The impact of E-learning in medical education. *Acad Med* 2006;81(3):207-12. [published Online First: 2006/02/28]
32. Link TM, Marz R. Computer literacy and attitudes towards e-learning among first year medical students. *BMC Med Educ* 2006;6:34. doi: 10.1186/1472-6920-6-34 [published Online First: 2006/06/21]
33. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013: new guidance for content of clinical trial protocols. *Lancet* 2013;381(9861):91-2. doi: 10.1016/S0140-6736(12)62160-6 [published Online First: 2013/01/12]
34. Medical Schools Council. Medical Schools [Available from: http://www.medschools.ac.uk/Students/Courses/Pages/All-courses.aspx.
35. Anderson F, Downing GM, Hill J, et al. Palliative performance scale (PPS): a new tool. *J Palliat Care* 1996;12(1):5-11. [published Online First: 1996/01/01]
36. Sessler CN, Grap MJ, Brophy GM. Multidisciplinary management of sedation and analgesia in critical care. *Semin Respir Crit Care Med* 2001;22(2):211-26. doi: 10.1055/s-2001-13834 [published Online First: 2005/08/10]
37. Weiss DJ, Shanteau J. CWS: A user's guide 2002 [Available from: http://www.ksu.edu/psych/cws/pdf/using_cws.pdf.

38. Cohen J. A power primer. *Psychological bulletin* 1992;112(1):155.
39. Bland JM, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. *The lancet* 1986;327(8476):307-10.

Acknowledgements

The authors would like to thank Olivia Baker and Sean O'Donnell for reviewing the study recruitment documents and providing valuable feedback.

Contributors

PS & PH conceived the idea for the study. NW produced an initial draft of the protocol and LO, NW and PS formed the working group that refined the study protocol and set up the study. All other members of the Trial Management Group (PH, SY, CT, FR and HG) provided input in the protocol design and study logistics. NW and PH were involved with developing the intervention. CT developed the study website. SY provided input for the recruitment strategies. FR devised the statistical analysis plan with input from HG. LO is the trial manager, PS is the guarantor of the study.

Funding

This work is supported by the Marie Curie I-CAN-CARE Programme grant (MCCC-FPO-16-U). Prof Stone is supported by the Marie Curie Chair's grant (MCCC-509537). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests

None declared

Ethics approval

Approval was obtained from the UCL Research Ethics Committee (Chair's action) on 19th January 2018 and an amendment was approved on 21st February 2018 (project ID 8675/002).

Appendices:

- SPIRIT checklist
- Evidence of funding by Marie Curie
- Evidence of ethics approval UCL REC

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Available in trial register (NCT03360812)
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 and 24
	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	24

	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)	17-18
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	6
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)	6-7
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	8
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)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6, 8-9
	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)	13
	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	14
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)	9-13
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	14-15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15-16
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	15
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	15
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	15
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15-16
	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	9-13
	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	9, 16
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	19-20
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	16-17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
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	17-18
	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	19
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)	19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
	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	19-20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
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	20
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	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A

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.

BMJ Open

Protocol for the ORaCIES study: an Online Randomised controlled trial to improve Clinical Estimates of Survival using a training resource for medical students

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-025265.R1
Article Type:	Protocol
Date Submitted by the Author:	20-Nov-2018
Complete List of Authors:	Oostendorp, Linda; University College London, Marie Curie Palliative Care Research Department White, Nicola; University College London, Marie Curie Palliative Care Research Department Harries, Priscilla; Kingston University & St George's, University of London., Centre for Applied Health and Social Care Research (CAHSCR) Yardley, Sarah; University College London, Marie Curie Palliative Care Research Department; Central and North West London NHS Foundation Trust Tomlinson, Christopher; Imperial College London, Bioinformatics Data Science Group; University College London, Marie Curie Palliative Care Research Department Ricciardi, Federico; University College London, Marie Curie Palliative Care Research Department; University College London, Department of Statistical Science Gokalp, Hulya; Brunel University Department of Clinical Sciences; Ondokuz Mayis Universitesi, Department of Electrical and Electronic Engineering Stone, Patrick; University College London, Marie Curie Palliative Care Research Department
Primary Subject Heading:	Palliative care
Secondary Subject Heading:	Medical education and training, Oncology
Keywords:	Prognosis, End of Life, PALLIATIVE CARE, online training resource, medical students, randomised controlled trial

Study protocol

Protocol for the ORaClES study: an Online Randomised controlled trial to improve Clinical Estimates of Survival using a training resource for medical students

Linda JM Oostendorp,[1*] Nicola White,[1*] Priscilla Harries,[2] Sarah Yardley,[1,3] Christopher Tomlinson,[1,4] Federico Ricciardi,[1,5] Hülya Gökalp,[2,6] Patrick Stone[1]

* These authors contributed equally to this work

[1] UCL, Marie Curie Palliative Care Research Department, Division of Psychiatry, University College London, London, United Kingdom;

[2] Centre of Health and Social Care Research, Faculty of Health and Social Care, Kingston University and St. George's, University of London, United Kingdom, formerly of Department of Clinical Sciences, Brunel University London, , London, United Kingdom;

[3] Central and North West London NHS Foundation Trust, London, United Kingdom;

[4] Bioinformatics Data Science Group. Imperial College London, London, United Kingdom

[5] Department of Statistical Science, University College London, London, UK;

[6] Ondokuz Mayis University, Department of Electrical and Electronic Engineering, Samsun, Turkey, formerly of Department of Clinical Sciences, Brunel University London, London, United Kingdom.

Correspondence to: Dr Linda Oostendorp: l.oostendorp@ucl.ac.uk

ABSTRACT

Introduction: Clinicians often struggle to recognise when palliative care patients are imminently dying (last 72 hours of life). A previous study identified the factors that expert palliative care doctors (with demonstrated prognostic skills) had used, to form a judgement about which patients were imminently dying. This protocol describes a study to evaluate whether an online training resource showing how experts weighted the importance of various symptoms and signs can teach medical students to formulate survival estimates for palliative care patients that are more similar to the experts' estimates.

Methods and analysis: This online double-blind randomised controlled trial will recruit at least 128 students in the penultimate or final year of medical school in the UK. Participants are asked to review three series of vignettes describing patients referred to palliative care and provide an estimate about the probability (0-100%) that each patient will die within 72 hours. After the first series, students randomised to the intervention arm are given access to an online training resource. All participants are asked to complete a second series of vignettes. After two weeks, all participants are asked to complete a third series. The primary outcome will be the probability of death estimates (0-100%) provided by students in the intervention and control arms for the second series of vignettes. Secondary outcomes include the maintenance effect at two week follow-up, weighting of individual symptoms and signs, and level of expertise (discrimination and consistency).

Ethics and dissemination: Approval has been obtained from the UCL Research Ethics Committee (8675/002) and local approvals will be obtained as appropriate. Results will be published in peer-reviewed journals using an open access format and presented at academic conferences. We will also publicise our findings on the Marie Curie website.

Trial registration number: Clinical Trials.gov NCT03360812; pre-results

Keywords (3-6): Prognosis, End of Life, Palliative care, online training resource, medical students, randomised controlled trial

Strengths and limitations of this study

- This is an evaluation of a novel training resource for improving prognostic skills in recognising palliative care patients who are imminently dying.
- A multicentre randomised controlled trial design has been used, with (partial) blinding of participants and researchers and including a follow-up to test for any maintenance effects.
- This study will provide evidence about whether an online training resource can influence how medical students make prognostic decisions in an experimental setting, using a prognostic task that may lack some ecological validity since it relies on an online rather than a face-to-face assessment of palliative care patients. Therefore, further testing of the intervention in routine medical education and assessment of the accuracy of clinicians' performance in real-world prognostic tasks will be required.

INTRODUCTION

When living with an incurable disease that shortens life expectancy, many patients and their relatives wish to receive information on what the future might bring, including a time frame of the expected length of survival.[1 2] Several reports on care near the end of life have highlighted that recognition of the dying phase in palliative care patients is inaccurate, and that this can have a significant negative impact on patient care at the end of life.[3-5] Being aware that death is imminent can help patients, families, and professionals to engage in discussions about goals of care and make decisions about appropriate care and treatment, including hospice admission and starting end-of-life care plans.[6 7] In addition, better prognostic awareness can shift patients' preferences from aggressive life-prolonging treatments towards comfort-oriented care.[7-10] It can also help patients and families to make plans for the time remaining, and discuss practical issues such as estate management and funeral planning.[7] For families, information about imminent death can help to make decisions about how to look after their loved one, for example deciding whether the patient can remain at home or deciding whether to stay overnight or invite other relatives to visit.[7]

While some prognostic models are available, in daily clinical practice it is usually the responsibility of a clinician to formulate a survival estimate.[11 12] Making accurate survival predictions is notoriously difficult, estimates are often overoptimistic and prognostic skills do not necessarily develop over time.[13-15] Many doctors try to avoid prognostication and feel insufficiently prepared to perform this clinical task.[16] The European Association for Palliative Care (EAPC) has recommended that training could improve the accuracy of clinicians' survival estimates, but there was little evidence to support this recommendation.[17] Virtually no education or training resources are available to specifically improve prognostic skills and a better understanding of how clinicians formulate their predictions is crucial to develop such resources.

This study will describe and evaluate an intervention for predicting imminent death (i.e. death within 72 hours). Given the current lack of training resources to improve prognostic performance, this

study will, as a proof of principle, focus on medical students who have limited clinical experience so that any effects of the intervention are more likely to be detected.

The intervention

The development of the training resource was informed by Social Judgement Theory, which assumes that judgements (prognostic decisions) result from the integration of different types of information, known as "cues".[18] Judgement analysis attempts to capture an expert's "judgement policy" using a multiple regression procedure to calculate the relative weights that the experts attach to different cues. In a previous study, we have used judgement analysis[19] to identify the clinical cues (e.g. breathing pattern and the presence of respiratory secretions) that expert clinicians use to formulate a prognosis of imminent death.[20] The training resource will provide students with task information on how to use the most important cues when making prognostic decisions. Outside of the palliative care context this approach has been used successfully to train a variety of other student populations about how to make decisions more aligned to those of experts.[21-24]

Experts can be identified in several ways.[25] In our previous study, expert palliative care doctors were selected based on the validity of their judgements.[26] Palliative care doctors were asked to complete an online prognostic test consisting of a series of vignettes based on real cases and their prognostic estimates were compared against actual survival. The top 20% of performers were defined as 'experts' and were invited to complete a second series of fictional vignettes. We will evaluate students' prognostic performance by comparing students' estimates against the estimates provided by the experts for the same series of fictional vignettes. In addition, to gain a fuller picture of the expertise as demonstrated by the students, we will assess the extent to which they are able to discriminate between patients with different severities of symptoms/signs and to consistently make similar prognostic decisions for patients with similar symptoms/signs.[25] It is important to note however that high levels of discrimination and consistency do not guarantee accuracy,[27] therefore

these results will be evaluated in conjunction with the comparison of students' estimates against the experts' estimates.

In addition to assessing whether students are able to follow the expert judgement policy, a follow-up assessment will be included where students are not given access to the training resource to assess whether they have learnt the policy. A relatively short interval of two weeks was chosen to minimise the risk of attrition, based on our experience with a previous study evaluating a similar training resource that showed 10% attrition at the two week follow-up, even though participants received a financial reward on completion.[22]

The training resource will be offered to study participants in an online format, which will enable easy access at the students' convenience, regardless of geographical location.[28-30] If the training material is found to be successful, the online format will enable widespread dissemination and facilitate easy updating and students will be able to re-access the information as and when required.[28] [31] Studies have indicated that e-learning in medical education, as a supplement to traditional ways of teaching, is perceived as acceptable and evaluated as useful by students.[31] [32]

Objectives

The aim of this trial is to evaluate whether an online training resource can teach medical students to model the prognostic decisions of expert palliative care doctors about which palliative care patients are likely to die within 72 hours. This study will:

- Assess if the probability of death estimates formulated by medical students become more similar to experts' estimates after completing an online training resource (primary objective);
- Determine if any effect of the online training resource is maintained after two weeks;
- Evaluate if the online training resource changes the weighting of individual symptoms/signs, and whether the students' judgement policies become more similar to the experts' judgement policies.

- Assess if the online training resource improves the expertise of the medical students, in terms of the ability to discriminate between patients and be consistent in decisions.

Trial design

This is an online multicentre double-blind randomised controlled trial involving an intervention arm that will receive an online training resource for prognostication and a control arm. Medical students will be randomised to these two parallel arms using a 1:1 allocation ratio. Since this will be the first trial of an intervention to improve prognostic skills, the study is designed as a proof of principle study, evaluating whether the training resource can influence how medical students make prognostic decisions in an experimental setting.

METHODS AND ANALYSIS

This protocol follows guidance from the SPIRIT 2013 statement,[33] and the completed SPIRIT checklist is available as an online supplementary file.

Study setting

This study will be conducted online using a purpose-built study website hosted by UCL. The study will recruit students from up to 33 medical schools in the United Kingdom, approved by the Medical Schools Council.[34] As we are offering a financial incentive for participating, it is important to control the potential total number of participants. We will approach individual medical schools as needed until the sample size has been achieved.

Eligibility criteria

Eligible participants should (1) be over 18 years of age; (2) be enrolled on a registered medical course within the UK; (3) be in the penultimate or final year of the course; (4) have sufficient English language proficiency; and (5) be willing and able to provide consent as indicated by taking part in the online study assessments. Students in the penultimate and final year are felt to have sufficient knowledge to understand the terminology in the vignettes and will have had at least one year of clinical experience as part of their training. Recruitment strategies will be targeted at students in the penultimate and final year of participating medical schools to minimise the risk of non-eligible students taking part. Participants will be asked to confirm their eligibility.

Intervention

The intervention is a newly developed online training resource to improve the recognition of imminent death in palliative care patients. The content was based on a previous study in which we used judgement analysis[19] to identify the clinical cues that expert palliative care doctors use to formulate a prognosis of imminent death in terminally ill inpatients.[20] Experts were presented with 50 vignettes

describing hypothetical palliative care patients (see Figure 1 for a sample vignette). There were seven symptoms and signs ('cues') available in each vignette: (1) Palliative Performance Scale (PPS) score[35]; (2) Richmond-Agitation Sedation Scale (RASS)score[36]; (3) rate of decline in general condition; (4) breathing pattern; (5) respiratory secretions; (6) urine output; and (7) peripheral cyanosis. The first four cues were the most heavily weighted in the decision making process of the experts.[26]

Study participants will be presented with the same vignettes and cues that had been presented to the expert palliative care doctors in the previous study. The online training resource will educate the participants on how to use the cue information when formulating a prognosis of imminent death, providing a description of the four most important cues and, where possible, graphical information for ease of understanding. The intervention will be implemented via the study website and should take approximately 15 minutes to complete.

Data collection procedure and outcomes

The data collection procedure is shown in the study flow diagram in Figure 2. After obtaining informed consent, participants will be asked a number of questions to obtain a description of the sample and enable subgroup analyses. This includes demographic questions (age, gender, ethnicity), course detail (place of study, year of study), and palliative care experience (training, placements, experience, confidence). Participants are asked for their name and university email address (to be entered twice for validation). This will allow them to log out and return to the same place at a more convenient time, which is hoped to reduce attrition. It will also allow the research team to check whether participants are affiliated with the universities the study is recruiting from, to populate the certificate of participation, and to send out reminders and gift vouchers.

Participants will then be randomised to either the intervention arm or control arm. Next, participants are given instructions, and are reminded to complete the study individually, in a quiet location, free from distraction at a time and place of their choosing. Following this, they will be able to complete a practice vignette to familiarise themselves with the online environment.

All participants will then be asked to review a first series of 40 vignettes. Each vignette will present a description of a patient (the stem), which is identical for each vignette, with seven cues that describe differing severities of symptoms or signs that vary between vignettes (see Figure 1). Participants will be asked to provide a percentage estimate of the probability that the patient will die within 72 hours (0% means no chance of death and 100% means certain death). This series of 40 vignettes includes 30 vignettes presented in random order for each participant, followed by 10 repeated vignettes, also in random order. These repeated vignettes are included to assess participants' level of expertise, as measured by the discrimination and consistency of probability of death estimates.[37] The order in which the seven cues are presented are also randomised per participant, to prevent order effects.

Participants in the intervention arm will then receive the online training resource, while participants assigned to the control group will not receive this additional information but will be informed that they are approximately half way through the study. All participants will be asked to provide probability of death estimates for a further series of 26 vignettes (including six repeated vignettes), in the same format as the first series of vignettes. The participants in the intervention arm will be able to access the online training resource during this second series of vignettes should they wish to do so. It is estimated that it will take up to 45 minutes to complete the first and second series of vignettes.

Two weeks after completing the second series of vignettes, participants will be asked to repeat the second series of 26 vignettes, although they will not be informed that the cases are the same as those that they have previously completed. Again, the vignettes will be presented in random order to minimise the risk of participants remembering vignettes or the estimates they provided previously. Participants in the intervention arm will not be given access to the online training resource on this occasion. This will enable us to determine if the effect of the intervention has lasted over time. It is estimated that this assessment will take up to 15 minutes to complete.

All participants can log out from the study website and return at a later time, at any point through the trial. Participants will be sent a reminder email when the third series of vignettes is due and if they start but do not finish the study. Participants will have a four week time window to complete the first and second series of vignettes, and another four week time window to complete the third series of vignettes. The web-based system will track the time students spend on completing the vignettes and the online training resource, if applicable. To improve data quality, drop-down lists are used where possible and participants will not be able to move on to the next page if essential information is missing or if information has been entered in an incorrect format. The online environment will be piloted by the study team.

Primary outcome

The primary outcome will be the continuous probability of death estimates (0-100%) provided from the students for the second series of vignettes.

Secondary outcomes

a. The maintenance effect will be measured by using the probability of death estimates as described for the primary outcome measure at the two week follow-up time point.
b. Cue weighting of the individual students will be compared against that of the experts. When students provide a probability of death estimate they weigh information or "cues" from the vignette as part of the process. By asking students to make a number of decisions on a series of vignettes in which cue values are varied, it is possible to model the weights assigned to the various cues.
c. The level of expertise will be assessed with the Cochran-Weiss-Shanteau (CWS) index of expertise.[25] The CWS index captures the degree of expertise demonstrated in a set of responses and consists of the ratio of discrimination to inconsistency.[37] This will help us to understand if the participants become better at discriminating between patients after the intervention, and if their prognostic decisions become more consistent.

Sample size

A sample of 128 subjects (64 subjects in each group) is required to detect a medium effect size (Cohen's d = 0.5) between the intervention and control groups, assuming a common standard deviation, 80% power and using a two sample t-test at the 5% significance level. A medium effect size of 0.5 is described as an effect that is likely to be visible.[38] Larger effect sizes were achieved in previous evaluation studies of similar online training resources by one of the members of our study team (PH).[22-24] We estimate that it will be necessary to recruit approximately 183 subjects in order to obtain a final sample size of 128 participants with complete data sets for analysis. The anticipated 30% drop-

out rate (i.e. participants who start but do not complete the task) has been estimated on the basis of previous similar studies by our own group. Recruitment will start from April 2018 and we anticipate to complete recruitment by the end of December 2018.

Recruitment

Recruitment strategies will differ slightly between medical schools to comply with local ethical/governance requirements. These methods may include: 1) The palliative care lead at each participating medical school introducing the study to students; 2) The course leader or administrator at each participating medical school distributing an email to all penultimate and final year students; and (3) Advertising the study using newsletters, virtual notice boards and student associations. The study recruitment materials will show the link to the study website and the study email address for students to contact the study team.

Randomisation and blinding procedures

Participant randomisation will be undertaken automatically through the web-based system using a pre-generated randomisation list with a block size of 10. This list will be generated by a member of the study team who will not be involved in recruitment (CT), using computer-generated random numbers.

Researchers and participants will be blinded as far as possible. For data monitoring purposes, researchers will be able to check how many participants are randomised to each arm, but will be blinded to which arm will be the intervention arm. All other data that could reveal the allocation (e.g. time taken to complete the intervention) will be concealed from the researchers who will be monitoring the data (NW and LO) and the statistician who will conduct the analysis (FR). The allocation will remain concealed until the statistician has completed the analysis. Participants will be partially blinded to the nature of the intervention and the randomised controlled design of the study to minimise attrition in the control group. Rather than telling participants that half will receive the

intervention and half will not, we will inform students that they will receive an online training resource in one of two different formats.

Inducements for participation

As a gesture for the time taken to complete the study and to promote participant retention, participants will be offered a total of £30 gift vouchers for completing the study. Participants will be offered a £10 gift voucher for completing the first stage of the study and a £20 gift voucher for completing the two week follow-up. The study will be open for new participants until 64 complete cases are available in each group. When recruitment closes, students who have started the study will be able to complete the remaining assessments and will be eligible to receive the vouchers. Participants who complete the research will receive a certificate of completion that will add towards their academic portfolio. Taking part in the study will give each participant an opportunity to develop some of the clinical skills required to recognise dying palliative care patients. If the resource is found to be effective, then this could benefit future medical students and palliative care patients.

Patient and public involvement We involved two medical students in the design of the study, to make sure the research design is appropriate for this population and the study documents are easy to understand. Two fourth-year medical students reviewed the recruitment documents and piloted the website, keeping track of how much time was needed to complete the study. Both students provided valuable comments, resulting in several changes in the recruitment email, advertisement material, and participant information sheet. These changes mainly involved emphasising certain aspects of the study to make it more appealing to medical students. One of these students will also be involved in distributing recruitment emails.

Statistical methods

Demographic characteristics, course detail and palliative care experience will be summarized by treatment assigned and overall. As a result of the randomisation process, we expect the groups to be balanced. Categorical data will be presented as numbers and percentages. Continuous data will either be described with mean and standard deviation, or median and interquartile range, pending the distribution. We will produce a CONSORT flow diagram of all participants (http://www.consort-statement.org/).

In this proof of principle study, we are seeking to evaluate whether an online training resource can influence how medical students make prognostic decisions in an experimental setting. Therefore, we will employ a per-protocol analysis where those participants who do not complete all vignettes or violate the protocol (e.g. putting the same answer for every vignette) will be removed from the analysis. To assess if the online training resource affected the probability of death estimates provided, we will calculate the degree of agreement between the study participants' probability of death estimates for the first and second series of vignettes and the probability of death estimates obtained from the experts in our previous study. Suitable regression models will be fitted to estimate the effect of the intervention, comparing agreement with the experts for those who received it and those who did not. In addition to this, we will also visualise the degree of agreement in both groups for the first and seconds series of vignettes, using the Bland Altman method.[39]

The maintenance of the study effect will be measured by repeating the primary outcome analysis with the estimates from the two week follow-up time point. To assess whether the intervention altered the judgement policy of the participants, we will examine participants' cue weights for the three series of vignettes and correlate them with the expert's cue weights presented in the training information. The CWS performance index and the subcomponents discrimination and consistency will be compared between the intervention and control arms for the three series of vignettes.[25 37]

Data monitoring and adverse events

Throughout the trial, the research team will review recruitment figures. Researchers will check the responses given by the participants, and the time taken by each participant to complete the vignettes, to assess for compliance with the protocol. Participants may be excluded from the analysis if their response record strongly suggests that they did not comply with the study protocol (e.g. all items answered with the same response or too speedily). The Trial Management Group (PS, PH, LO, NW, CT, SY, FR, HG) will be responsible for overseeing the trial and will meet regularly (at least four times per year) to review recruitment figures.

This is a very low risk study. Students will have had at least one year of clinical experience as part of their training, and are informed that the vignettes are hypothetical. In the Participant Information Sheet students are encouraged to contact the student support services at the medical school they attend if they do experience psychological distress. This study will not have a Data Monitoring Committee.

ETHICS AND DISSEMINATION

Approval has been obtained from the UCL Research Ethics Committee (8675/002) and local approvals will be obtained as appropriate. In case any protocol amendments are required, these will be reviewed by the Trial Management Group before submission to the relevant committees, and the trial registry will be informed where necessary.

Consent

Participants will be given a brief summary of what the study involves in the recruitment email. On the website, there will be a welcome page with information about the study and the Participant Information Sheet is available to download. However, as described above, participants will be partially blinded to the nature of the intervention and the randomised controlled design of the study. The participants will be reminded that they are free to withdraw at any time. Informed consent will be obtained via two checkboxes before starting the study assessments: (1) to participate; and (2) to acknowledge the results will be used in future publications, research and educational packages. Those who do not consent will not be able to continue to the next page.

On completion of the second and third series of vignettes, a debrief page will be shown to remind the participant what the results will be used for. The contact details for the study team will also be displayed should they have any concerns or issues they wish to follow-up. This debrief will not include any more detailed explanation of the two groups students were randomised to or the active intervention, as we feel this would not be appropriate. Students will participate at a time convenient to them, and we would not want students who have completed the study to disclose this information to others who have yet to participate.

Data management

Our study received ethics approval before the introduction of the GDPR on 25th May 2018. The documents that were approved state that all data will be handled in accordance with the UK Data

Protection Act 1998. No formal amendment was required following the introduction of the GDPR, but we added a transparency message to the study website to make participants aware of how we will use their information. Participants will be asked for their names and university email address as a personal identifier as well as being assigned a unique participant ID. During the trial, all data will be kept securely on a web-based database, which is encrypted and password protected. The database will be accessible to approved members of the research team only as access to the intranet will be restricted to their IP addresses only. Recruitment strategies may include the study being introduced to students by their local palliative care lead. This person will not have access to the study database and will therefore not be aware which students participated and which did not, nor will he or she have access to the prognostic performance data of individual students.

Once all data have been reviewed and the gift vouchers have been distributed, the names and email addresses will be deleted from the web-based database in a secure manner and only the participant ID will be referenced. The final trial database will be downloaded from the website by the research team for statistical analysis and UCL will act as the data controller of such data for the study.

Dissemination policy

Study results will be published in peer-reviewed, indexed journals using an open access format, and the results will be presented at academic conferences. Authorship eligibility will be in accordance with The International Committee of Medical Journal Editors. We will also publicise our findings on the Marie Curie website. If the online training resource is proven effective, it will be made freely available after the trial. Data (suitably anonymised) may be shared with other research groups if a reasonable request is submitted to and agreed by the CI.

REFERENCES

1. Parker SM, Clayton JM, Hancock K, et al. A systematic review of prognostic/end-of-life communication with adults in the advanced stages of a life-limiting illness: patient/caregiver preferences for the content, style, and timing of information. *J Pain Symptom Manage* 2007;34(1):81-93. doi: 10.1016/j.jpainsymman.2006.09.035 [published Online First: 2007/05/29]
2. Steinhauser KE, Christakis NA, Clipp EC, et al. Factors considered important at the end of life by patients, family, physicians, and other care providers. *JAMA* 2000;284(19):2476-82. [published Online First: 2000/11/14]
3. Neuberger J. More care, less pathway: a review of the Liverpool Care Pathway. *Department of Health* 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/212450/Liverpool_Care_Pathway.pdf.
4. Parry R, Seymour J, Whittaker B, et al. Rapid evidence review: pathways focused on the dying phase in end of life care and their key components. *Nottingham: University of Nottingham and the NHS End of Life Care Programme* 2013;5
5. Leadership Alliance for the Care of Dying People. One chance to get it right: Improving people's experience of care in the last few days and hours of life. 2014. http://wales.pallcare.info/files/One_chance_to_get_it_right.pdf.
6. Kiely BE, Stockler MR, Tattersall MH. Thinking and talking about life expectancy in incurable cancer. *Semin Oncol* 2011;38(3):380-5. doi: 10.1053/j.seminoncol.2011.03.007 [published Online First: 2011/05/24]
7. Glare PA, Sinclair CT. Palliative medicine review: prognostication. *J Palliat Med* 2008;11(1):84-103. doi: 10.1089/jpm.2008.9992 [published Online First: 2008/03/29]
8. Mack JW, Weeks JC, Wright AA, et al. End-of-life discussions, goal attainment, and distress at the end of life: predictors and outcomes of receipt of care consistent with preferences. *J Clin Oncol* 2010;28(7):1203-8. doi: 10.1200/JCO.2009.25.4672 [published Online First: 2010/02/04]
9. Weeks JC, Cook EF, O'Day SJ, et al. Relationship between cancer patients' predictions of prognosis and their treatment preferences. *JAMA* 1998;279(21):1709-14. [published Online First: 1998/06/12]
10. Wright AA, Zhang B, Ray A, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. *JAMA* 2008;300(14):1665-73. doi: 10.1001/jama.300.14.1665 [published Online First: 2008/10/09]
11. Woelk CJ. How long have I got? *Can Fam Physician* 2009;55(12):1202-06.
12. Tanneberger S, Malavasi I, Mariano P, et al. Planning palliative or terminal care: the dilemma of doctors' prognoses in terminally ill cancer patients. *Ann Oncol* 2002;13(8):1320-2; author reply 22-3. [published Online First: 2002/08/16]
13. Glare P, Sinclair C, Downing M, et al. Predicting survival in patients with advanced disease. *European Journal of Cancer* 2008;44(8):1146-56.
14. White N, Reid F, Harris A, et al. A systematic review of predictions of survival in palliative care: How accurate are clinicians and who are the experts? *PloS one* 2016;11(8):e0161407.
15. Glare P, Virik K, Jones M, et al. A systematic review of physicians' survival predictions in terminally ill cancer patients. *BMJ* 2003;327(7408):195-8. doi: 10.1136/bmj.327.7408.195 [published Online First: 2003/07/26]
16. Christakis NA, Iwashyna TJ. Attitude and self-reported practice regarding prognostication in a national sample of internists. *Arch Intern Med* 1998;158(21):2389-95. [published Online First: 1998/11/25]

17. Maltoni M, Caraceni A, Brunelli C, et al. Prognostic factors in advanced cancer patients: evidence-based clinical recommendations—a study by the Steering Committee of the European Association for Palliative Care. *Journal of Clinical Oncology* 2005;23(25):6240-48.
18. Cooksey RW. The Methodology of Social Judgement Theory. *Thinking & Reasoning* 1996;2(2-3)
19. Cooksey RW. Judgment analysis: Theory, methods, and applications. San Diego, CA, US: Academic Press 1996.
20. How to Identify Doctors who Are Best at Recognising Dying Patients. EAPC 2017 15th World Congress of the European Association for Palliative Care; 2017; Madrid, Spain.
21. Wigton RS, Poses RM, Collins M, et al. Teaching old dogs new tricks: using cognitive feedback to improve physicians' diagnostic judgments on simulated cases. *Academic Medicine* 1990;Sep;65(9 Suppl):S5-6.
22. Harries P, Tomlinson C, Notley E, et al. Effectiveness of a decision-training aid on referral prioritization capacity: a randomized controlled trial. *Medical Decision Making* 2012;32(6):779-91.
23. Harries P, Davies M, Gilhooly K, et al. Educating novice practitioners to detect elder financial abuse: a randomised controlled trial. *BMC medical education* 2014;14(1):21.
24. Harries P, Unsworth C, Gokalp H, et al. A randomised controlled trial to test the effectiveness of decision training on assessors' ability to determine optimal fitness-to-drive recommendations for older or disabled drivers. *BMC Med Educ* 2018;18(1):27. doi: 10.1186/s12909-018-1131-4 [published Online First: 2018/02/15]
25. Weiss DJ, Shanteau J. Empirical assessment of expertise. *Hum Factors* 2003;45(1):104-16. doi: 10.1518/hfes.45.1.104.27233 [published Online First: 2003/08/15]
26. How Is Imminent Death Recognised? A Study to Understand the Decision Making Process of Expert Prognosticators. 10th World Research Congress of the European Association for Palliative Care (EAPC); 2018; Bern, Switzerland.
27. Weiss DJ, Shanteau J, Harries P. People Who Judge People. *J Behav Dec Making* 2006;19:441–54.
28. Choules AP. The use of elearning in medical education: a review of the current situation. *Postgrad Med J* 2007;83(978):212-6. doi: 10.1136/pgmj.2006.054189 [published Online First: 2007/04/04]
29. McKimm J, Jollie C, Cantillon P. ABC of learning and teaching: Web based learning. *BMJ* 2003;326(7394):870-3. doi: 10.1136/bmj.326.7394.870 [published Online First: 2003/04/19]
30. Ellaway R, Masters K. AMEE Guide 32: e-Learning in medical education Part 1: Learning, teaching and assessment. *Med Teach* 2008;30(5):455-73. doi: 10.1080/01421590802108331 [published Online First: 2008/06/26]
31. Ruiz JG, Mintzer MJ, Leipzig RM. The impact of E-learning in medical education. *Acad Med* 2006;81(3):207-12. [published Online First: 2006/02/28]
32. Link TM, Marz R. Computer literacy and attitudes towards e-learning among first year medical students. *BMC Med Educ* 2006;6:34. doi: 10.1186/1472-6920-6-34 [published Online First: 2006/06/21]
33. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013: new guidance for content of clinical trial protocols. *Lancet* 2013;381(9861):91-2. doi: 10.1016/S0140-6736(12)62160-6 [published Online First: 2013/01/12]
34. Medical Schools Council. Medical Schools [Available from: http://www.medschools.ac.uk/Students/Courses/Pages/All-courses.aspx.
35. Anderson F, Downing GM, Hill J, et al. Palliative performance scale (PPS): a new tool. *J Palliat Care* 1996;12(1):5-11. [published Online First: 1996/01/01]
36. Sessler CN, Grap MJ, Brophy GM. Multidisciplinary management of sedation and analgesia in critical care. *Semin Respir Crit Care Med* 2001;22(2):211-26. doi: 10.1055/s-2001-13834 [published Online First: 2005/08/10]
37. Weiss DJ, Shanteau J. CWS: A user's guide 2002 [Available from: http://www.ksu.edu/psych/cws/pdf/using_cws.pdf.

38. Cohen J. A power primer. *Psychological bulletin* 1992;112(1):155.
39. Bland JM, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. *The lancet* 1986;327(8476):307-10.

Acknowledgements

The authors would like to thank Olivia Baker and Sean O'Donnell for reviewing the study recruitment documents and providing valuable feedback.

Contributors

PS & PH conceived the idea for the study. NW produced an initial draft of the protocol and LO, NW and PS formed the working group that refined the study protocol and set up the study. All other members of the Trial Management Group (PH, SY, CT, FR and HG) provided input in the protocol design and study logistics. NW and PH were involved with developing the intervention. CT developed the study website. SY provided input for the recruitment strategies. FR devised the statistical analysis plan with input from HG. LO is the trial manager, PS is the guarantor of the study.

Funding

This work is supported by the Marie Curie I-CAN-CARE Programme grant (MCCC-FPO-16-U). Prof Stone is supported by the Marie Curie Chair's grant (MCCC-509537). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests

None declared

Ethics approval

Approval was obtained from the UCL Research Ethics Committee (Chair's action) on 19th January 2018 and an amendment was approved on 21st February 2018 (project ID 8675/002).

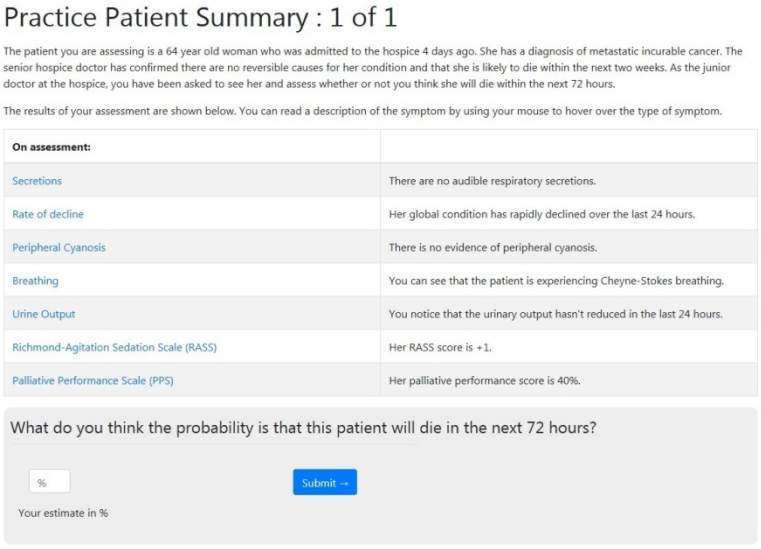
Appendices:

- SPIRIT checklist
- Evidence of funding by Marie Curie
- Evidence of ethics approval UCL REC

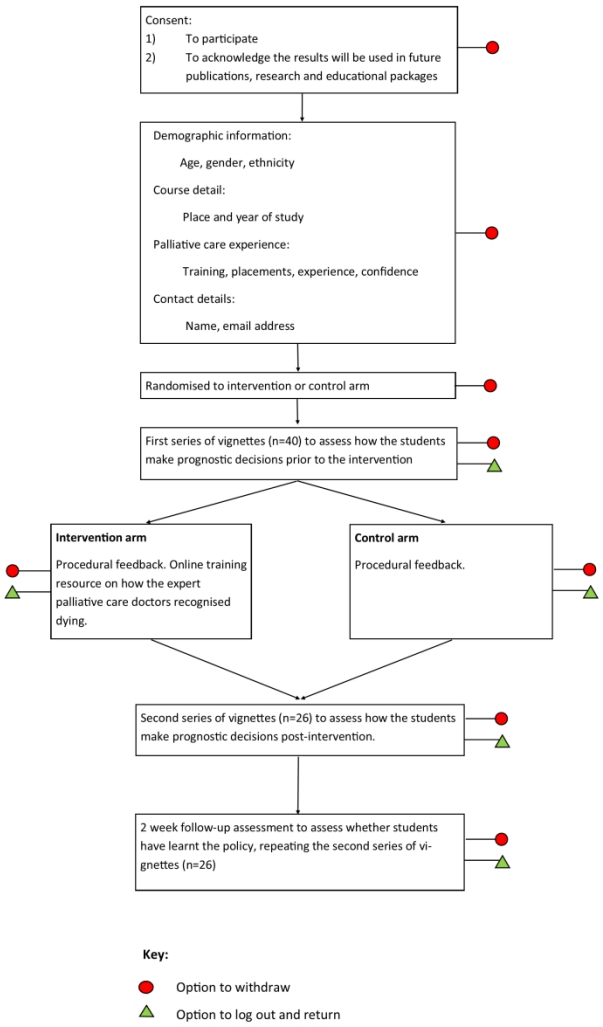
Figure 1 Sample vignette

Figure 2 Study flow diagram

Legend: Red – withdraw, Green – log out and return.



389x219mm (96 x 96 DPI)



Red – withdraw, Green – log out and return.

209x297mm (300 x 300 DPI)

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Available in trial register (NCT03360812)
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 and 22
	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	22

	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)	15-16
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	6-7
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)	7
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	8
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)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6, 8-9
	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)	14
	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	15
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)	9-14
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	12-13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	13-14
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	13-14
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	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13-14
	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	9-12
	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	13-14
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	17-18
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	14-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15-16
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	15-16
	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	17
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)	17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
	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	17-18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
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	18
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	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A

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.