STUDY PROTOCOL

ImproveCare - The management of clinical uncertainty in hospital settings

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ABSTRACT IN PLAIN ENGLISH

500,000 people die per year in the UK; half of all deaths occur in hospital. Most people prefer to die at home but this does not happen because there is little discussion between patients, families, and health care professionals about what they want. It is made worse when it is difficult for health care staff to identify patients, whose situation is clinically uncertain, an area of care many professionals do not possess enough knowledge/skills in. Recent reports have highlighted what can go wrong in the presence of clinical uncertainty and at the end of life; it can be devastating for patients and families. The AMBER care bundle (ACB) has been developed to care better for hospital patients whose situations are clinically uncertain and are at risk of dying during their hospital stay despite treatment. For these patients staff then develop a plan with patients (where possible) and their family that documents what is important to them. The patient's status and their wishes are revisited daily. We have conducted a small study to explore the ACB and observed some benefits and areas of concern. Before more hospitals use the ACB it is really important we rigorously study whether the ACB improves care, or not. We plan to conduct a feasibility study to compare ACB care with the usual care. The feasibility study will help us know if can recruit enough people, that the outcomes we use reflect what patients and families feel are important, and that the study procedures are workable. We will collect information from patients, their families and healthcare professionals at different time points. Open interviews with patients, caregivers and staff will help us better understand what they value about the ACB and how it works.

SCIENTIFIC ABSTRACT

STUDY AIM: To determine the feasibility of a pragmatic, multi-centre, cluster randomised controlled trial to optimise the design, and to define the outcomes, for a fully powered definitive trial of the AMBER care bundle versus standard care.

METHODS: **Design**: Following the Medical Research Council guidance for the development and evaluation of complex interventions, a feasibility cluster RCT, incorporating qualitative components across four district general hospitals (DGHs) in the UK, and economic modelling.

Patients: Patients in DGHs who are deteriorating, whose situations are clinically uncertain, with limited reversibility, and at risk of dying during their episode of care, despite treatment.

Measurement of outcomes & costs: We will optimise and refine the AMBER care bundle focusing on training, implementation and documentation. We will test our ability to recruit and consent participants. We will test our proposed primary outcome measure, the 'Patient/family anxiety and communication subscale', of the Integrated Palliative care Outcome Scale (I-POS). We will test our secondary outcomes that are included in the modified QUALYCARE postal survey. This examines quality of end of life care for patients/families including quality of information/communication. Health costs will examine health resources and costs to families. We will also measure the 'standard' or 'usual' care provided at the wards. Qualitative interviews will be

conducted with patients and caregivers to understand more about what they value most about AMBER care bundle and how it may be working.

BACKGROUND TO THIS STUDY

The magnitude of dying in hospital settings

Every year 500,000 people die in the UK [1]. Of these more than half occur in hospital [2]. This is not what patients and families want; 69.2% (51-84%) would prefer to die at home [3]. Most deaths are anticipated with up to 75% of all deaths expected so there is time for discharge to home or more familiar and preferred surroundings. But this is not implemented frequently enough; a major reason for hospital death is poor communication about declining health between patients and health care professionals [4] and poor identification and management of patients who situations are clinical uncertainty [5].

The potential for better care

Poor hospital care and inadequate communication, which include patient safety and adverse events, have received increasing attention, particularly among the frail elderly and the dying. The Francis Report [6], the Independent Review of Liverpool Care Pathway [7] and the recent Parliamentary and Health Services Ombudsman's report into complaints about end of life care [8] all highlight the devastating effect which poor communication and lack of honesty can have on patients and their families, towards the end of life. Research has also demonstrated that the costs of patient care in the last year of life are high [9]. Yet when specialist palliative care services are available in hospital and community settings, health service costs can be reduced and patient and family-centred outcomes improved [10-12].

In 2010 a London hospital identified inconsistencies in the quality of care for patients whose situations were clinically uncertain, for those who were deteriorating, and especially for those at the end of life [13]. Issues included inadequate decision-making and poor engagement with patients and carers. A potential solution was developed; the ***AMBER care bundle***[1]***.*** AMBER stands for:

[1] A 'care bundle' to be a set of evidence-based, or self-evident good-practice-based interventions for a defined patient population and care setting (1). They typically consist of a small number of interventions (normally 4–5), which when implemented together, are associated with improvements in clinical outcomes (2). **The AMBER care bundle makes clinical decision-making explicit in situations of uncertainty, by encouraging (i) the clinical team to develop and document, within a reasonable period of time, a clear medical plan in conjunction with the patient and their family, (ii) to consider anticipated outcomes, and (iii) resuscitation and escalation status**. The bundle is modelled on previous empirical work that includes: a literature review and examination of clinical records to determine need and to develop its theoretical underpinning. The AMBER care bundle represents a complex intervention in that it:

- Comprises multiple components and layers (identification, current and future care planning including escalation and de-escalation decisions, communication delivery, assessment of patient preferences and systematic follow up, acknowledging dynamic wishes and physical conditions);

(i) **A**ssessment;
(ii) **M**anagement;
(iii) **B**est practice;
(iv) **E**ngagement;
(v) **R**ecovery uncertain.

The AMBER care bundle aims to improve care for patients in the acute hospital setting who are deteriorating, whose situations were clinically uncertain, with limited reversibility, and at risk of dying during their hospital stay, despite treatment [13]. The AMBER care bundle is concerned with patients with more predictable progressive disease (i.e. advanced cancer) and also those with a less predictable course characterised by episodic acute deterioration (i.e. frail older patients). The AMBER care bundle follows an algorithmic approach to encourage clinical teams to develop and document a clear medical plan, considering anticipated outcomes and resuscitation and escalation status and revisiting the plan daily. The AMBER care bundle encourages staff, patients and families to continue with treatment in the hope of a recovery, while talking openly about preferences and priorities should the worst happen.

The intended benefits of the AMBER care bundle include: (i) increased and improved communication; (ii) enabling/supporting informed and shared decision making and choice during end of life care; (iii) improved patient/family-centred quality of life through reducing anxiety (iv) enabling home death if preferred; (v) supporting health professionals to develop knowledge, skills and confidence in end of life care delivery, and (vi) reducing unnecessary hospital admissions, while improving cost-effectiveness (reducing hospital length of stay) and making more efficient use of health services.

Why research is needed now

The AMBER care bundle has been identified by NHS England as one of five key enablers to *Transform End of Life Care in Acute Hospitals* [14] [15] and it is currently being used across a network for approximately 40 of hospitals including district general hospitals. Further rollout is planned. However, recommendation 7 from the Independent Review of the Liverpool Care Pathway states explicitly it is imperative that 'education/training methods and programmes addressing uncertainty and

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- Aims to change behaviours of health/social care professionals delivering the intervention by enhancing recognition of clinical uncertainty in clinical outcomes, patients in the last months of life and management and goals of care;
- Focuses on staff in primary, hospital and voluntary care, thus including different groups and organisational levels;
- Includes several complex intended outcomes, including changes in patient involvement in decision-making around situations of clinical uncertainty. It is tailored to individual patient and family need, and circumstances by those delivering the AMBER care bundle.

1. Resar, R., et al. *Using care bundles to improve health care quality. IHI Innovation Series white paper*. 2012 [cited 2014 05.12.14]; Available from: http://www.ihi.org/resources/Pages/IHIWhitePapers/UsingCareBundles.aspx
2. Robb, E., et al., *Using care bundles to reduce in-hospital mortality: quantitative survey.* British Medical Journal, 2010. **340**(c1234)

communication when caring for the dying are evaluated' [7]. It is imperative that a clinical trial of the AMBER care bundle take place to accurately quantify patient, clinician and health systems benefits, and that any harms are understood and managed [16].

Now, more than ever (with ageing populations and increasing numbers of people dying from cancer and non-malignant conditions [17]), health care systems should provide every patient and their family a dignified death [18]. Facing deteriorating health and uncertain recovery is distressing for patients who may be dying, and their families. This is particularly due to the frequent, possibly unnecessary, hospital admissions during the last year of life [19]; in England patients currently spend an average of 29.7 days of their 12 months in hospital [9]. This is costly for health services and for society. These concerns are endorsed by the NHS Commissioning Framework which includes two outcomes to improve care for people at the end of life; the proportion of patients who die in their preferred place of death; and bereaved relatives' experiences of care [20]. Interventional research, including an evaluation of the AMBER care bundle, aims to understand how these outcomes can be addressed.

How the existing literature supports this study

A small but growing body of evidence sheds light on processes and outcomes associated with the AMBER care bundle. Since its introduction at a major London hospital, inpatient deaths have declined (93-81 per month) [8]. A recent single centre study identified that rather than being used as a tool to identify patients with an uncertain recovery, the AMBER care bundle was principally used when it became certain that patients would not recover [5].

We conducted the first comparative observational mixed-methods study of the AMBER care bundle and identified a mixed picture [21]. First, the AMBER care was associated with increased frequency of discussions about prognosis between clinicians and patients, and higher awareness of their prognosis by patients. Second, we observed that for those patients who died in locations other than hospitals, shorter length stays were present than those who received usual care. The mean length of hospital stay for the patients supported by the AMBER care bundle was 20.3 days (range 1-87) compared to 29.3 days (range 6-70) in the comparison wards. The mean length of hospital stay for all patients who were discharged and died in a place **other than** hospital also differed; mean length of stay for AMBER care bundle was 17.6 [range 1-87) compared to 21.4 days (mean) (range 6-70) in the comparison wards. However, we identified whilst the instances of communication were greater, they were often associated with lower clarity in the relation to the quality of information transmitted about a patient's condition. Moreover, relatives who cared for dependants or loved one who were supported by the AMBER care bundle described more unresolved concerns about caring for them at home.

Whilst this evidence suggests potential benefits to care supported by the AMBER care bundle, it identifies downsides, specifically information and communication. Therefore clinical equipoise in relation to the AMBER care bundle still exists. The findings point to

a need for robust comparative evaluation of the AMBER care bundle. This will first be informed by a feasibility study.

Clinical uncertainty in hospital settings

Clinical uncertainty is not a simple concept and a situation of uncertainty usually results from several inter-related factors. Mishel was one of the first to develop an overarching theory of uncertainty in illness which aimed to explain the underlying processes governing patients' experiences of uncertainty [22]. Specifically, four concepts contribute to an uncertain state, including complexity, unpredictability, ambiguity, and lack of information [22-24]. McCormick further developed these ideas and described situations of uncertainty in terms of the probability of events occurring, the temporality of events, and individuals' perceptions of their situation [25].

If clinical uncertainty is not explicitly addressed, there are worse psychological outcomes for patients [26, 27]. Moreover, evidence suggests that, in the last 30 days of life, the combination of deteriorating health and clinical uncertainty are highly distressing for patients in hospital, and their families [28, 29]. This distress is amplified when discussions about their situation and preferences for care and location of death are absent; 67-80% of people want to be informed about poor prognosis [30]. However, research shows discussions about prognosis rarely occur [31], increasing the likelihood of hospital deaths, but also leading to poor satisfaction, mistrust, and loss of confidence in health care professionals [32-35]. Indeed, complaints about care at the end of life care in hospital settings are frequent [36].

Clinical uncertainty also impacts on clinicians' confidence and their practice. Clinicians frequently struggle with uncertainty, which can result in overtreatment or over-investigation [37], increased costs [27], and lack of communication with patients about their future [38, 39]. Further, clinicians often feel inappropriately trained to deal with uncertainty – only 4 of 21 UK postgraduate medical training curricula contain detailed recommendations and curriculum goals relevant to dealing with uncertainty. However, when situations of uncertainty are acknowledged and managed alongside high quality care and specifically at the end of life, collaborative decision-making is possible [40]. This empowers patients and their carers [41-43], and in turn leads to improved outcomes and increased satisfaction with care [44, 45].

AIM OF THIS FEASIBILITY STUDY

To determine the feasibility of a pragmatic, multi-centre, cluster randomised controlled trial to optimize the design, and to define the outcomes, for a fully powered definitive trial of the AMBER care bundle versus standard care.

Study objectives

1. To examine the extent to which the AMBER care bundle requires further refinement or adaptation (for example referral criteria to identify which patients would benefit most) to suit local conditions;

2. To assess the acceptability of the AMBER care bundle to patients, their families and health care professionals;

3. To determine the active ingredients of the AMBER care bundle which need to be maintained to ensure fidelity of the intervention for a full trial;

4. To assess compliance and barriers to the delivery of the AMBER care bundle;

5. To examine recruitment, retention and follow-up rates at both patient and cluster levels;

6. To test trial data collection measures and determine their optimum timing in a larger trial;

7. To provide a preliminary estimate of the effectiveness of AMBER care bundle compared with standard care to inform sample size calculation for the full trial;

8. To estimate the intra-cluster correlation coefficient and likely cluster size;

9. To assess the degree of contamination at a ward level due to 'between-ward' staff and patient movements;

10. To examine differences in the use of financial resources between the AMBER care bundle and standard care.

RESEARCH DESIGN

We will conduct a feasibility cluster randomised controlled trial with integrated (concurrent) qualitative components to deliver on our study objectives (in order to inform the design of a definitive clinical trial (refer to figure 1 below). Our approach closely follows the Medical Research Council guidance for developing and evaluating complex interventions [46] (refer to figure 2) and the MORECare Statement [47] for feasibility evaluations in end of life care. Specifically, the study makes use of several work components to refine the intervention and evaluate the feasibility trial of the AMBER care bundle:

1. The clinical trial of the patient supported by the AMBER care bundle compared to those cared for on control wards;

2. A follow-back, post bereavement survey of relatives or close friends of patients who fulfilled the criteria to be supported by the AMBER care bundle on intervention and control wards;

3. Qualitative interviews with patients and their relatives/close friends located on AMBER care bundle and control wards;

4. Non-participation observation work in multi-disciplinary teams based on the intervention and control wards;

5. Focus groups with health care professionals located on intervention and control wards;

6. A care questionnaire completed by the health care professionals located on intervention and control wards;

7. Case note reviews and heat maps produced retrospectively at each study ward.

Figure 1: Design of concurrent mixed methods design for the feasibility cluster RCT

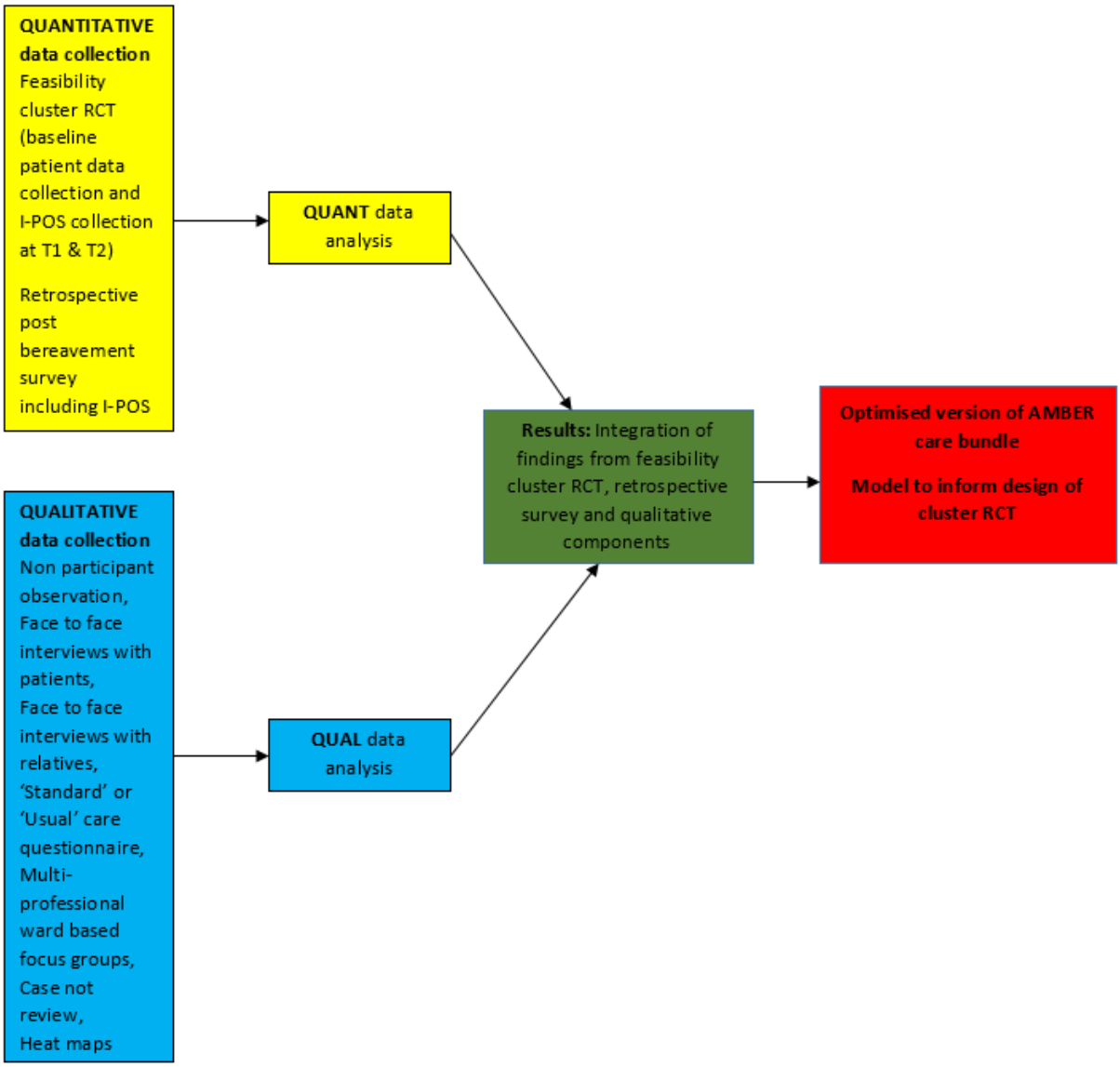
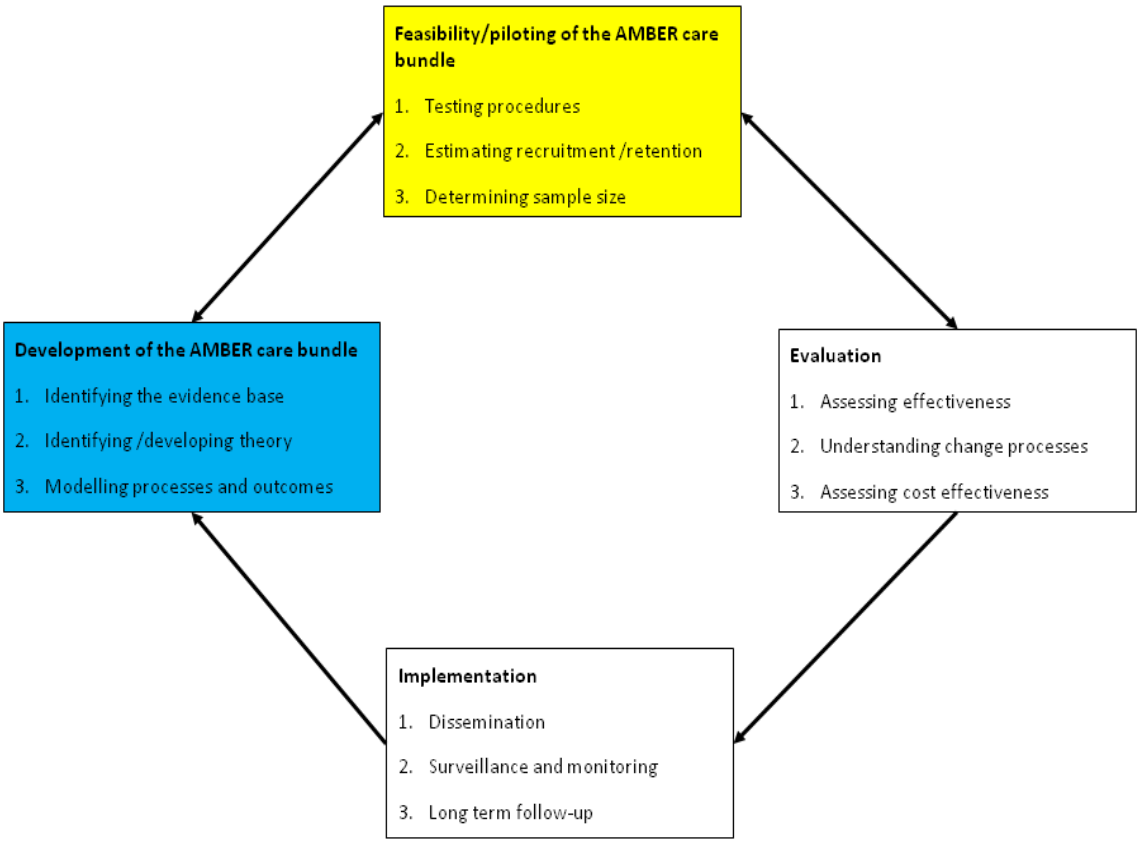


Figure 2: Conceptual framework for the evaluation of the AMBER care bundle showing which elements of the MRC framework have been completed (blue box) and those proposed for testing in this feasibility study (yellow box)



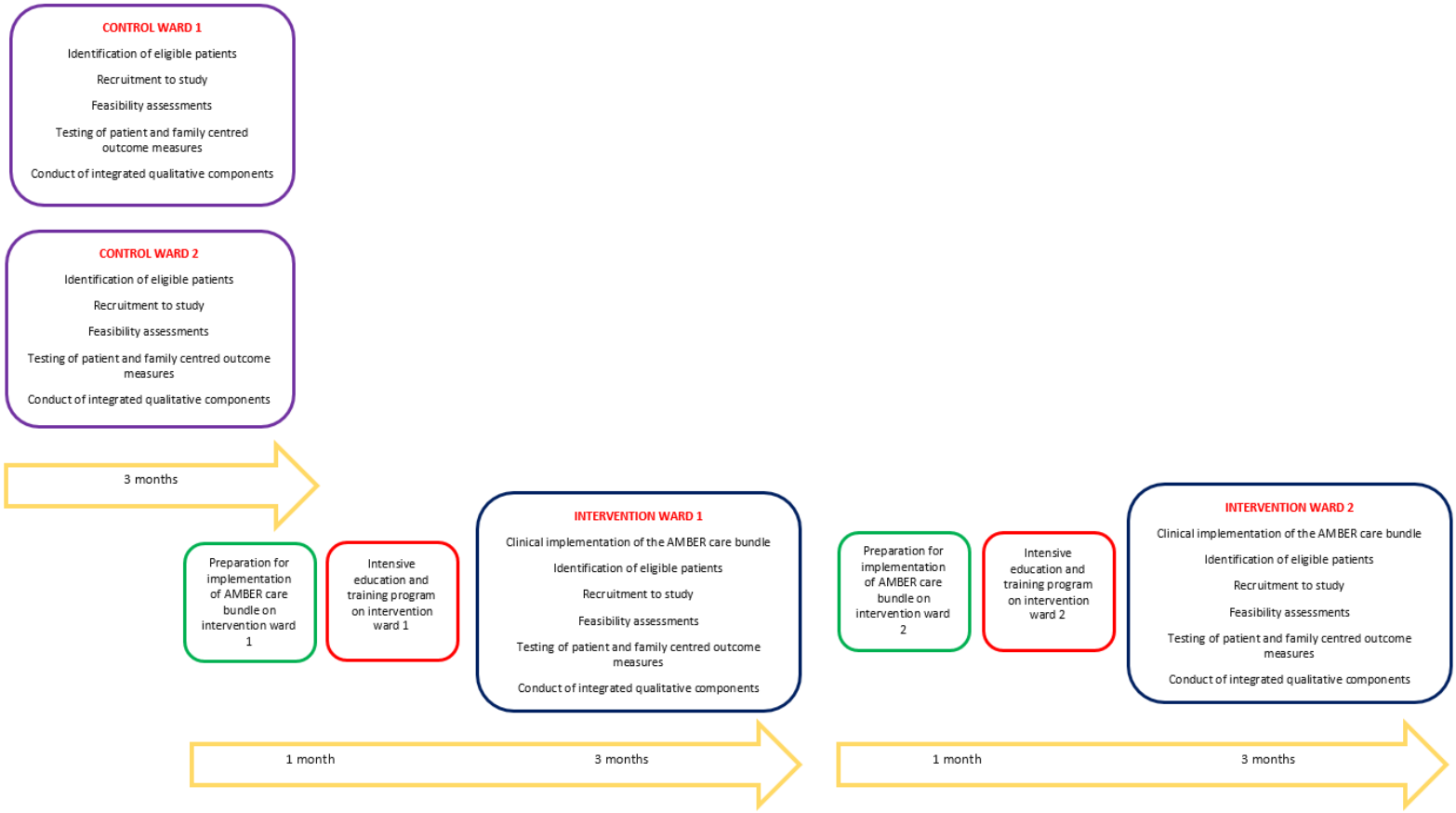
General planned procedures for the feasibility cluster randomised controlled trial

The organisation of the feasibility cluster RCT is modelled closely on a protocol of the effectiveness of the Liverpool Care Pathway [48].

To avoid the risk of contamination, each of the four hospitals will provide **one** eligible general medical ward. This feasibility study will take place firstly in two control wards at the same time, then each intervention ward opening sequentially. Eligible general medical wards will be randomised to receive the complex intervention (the AMBER care bundle) or no intervention at all i.e. continues to offer best usual care for the duration of the study. Immediately after randomisation the educator or ward manager responsible for the implementation of the AMBER care bundle on the intervention wards will complete the organisational procedures required for the implementation of the bundle. The research team will complete the data collection at two controls wards, while the implementation and training starts at the first intervention ward. Once the implementation and data collection are finished at the first intervention ward, the

nurse educator will move on to the second intervention ward. The data collection then will commence at the second intervention ward.

Figure 3: Timeframe for organisation of training for intervention wards and study recruitment and data collection points



THE STUDY SETTING AND PARTICIPANTS

Setting

This feasibility cluster randomised controlled trial will be set in **four district general hospitals (DGHs)**, that are defined as major secondary care facilities which typically provide an array of diagnostic and therapeutic services to local populations. There are over 250 DGHs in the UK [49]; they are therefore ideal and abundant settings in which to implement and test the effect of the AMBER care bundle; the findings from this feasibility study would inform future scalability. However, DGHs are extremely busy environments in which to conduct research, with patients being rapidly assessed and transferred from medical acute admissions units to other wards within the hospital. This makes it challenging to track study participants and obtain accurate reports of their condition or outcomes. For this reason we are mindful we must focus on **general medical wards** where patients whose conditions/situation are clinically uncertain, and where the most acute deteriorating patients, are cared for.

This study will be conducted across **four NHS DGHs (Chesterfield Royal Hospital, East Surrey Hospital, Maidstone and Tunbridge Wells NHS Trust and Northwick Park in North West London)**. These DGHs serve diverse populations including those that comprise ethnic diversity and material deprivation. The hospitals have differing strengths and weaknesses in terms of their Care Quality Commission ratings.

Patient inclusion criteria

In both arms of the study we will recruit patients (and where relevant their relatives) **who are facing clinical uncertainty as to recovery or continued deterioration increasing risk to end of life - but not clearly in the last few days of life - and for whom active medical management may still be appropriate**. In the intervention arm this comprises patients supported by the AMBER care bundle who the clinical staff have assessed met AMBER eligibility criteria detailed below. In the control wards, the AMBER eligibility criteria 1 and 2 are used only. This is a modification to the protocol following review of the eligibility criteria over a 4 month recruitment period. Application of the eligibility criterion 3 ‘patients at risk of dying’ in the control sites to identify patients requires a similar level of education and support as provided in the intervention site. Without this level of education and support there is wide variability on the interpretation of this criterion with tendency for prognostication rather than consideration of risk. However, providing this level of education and support would result in contamination in the control sites.

Identification of potential cases

Clinical staff in conjunction with research nurses will test out identifying patients on the control wards daily who fulfil the following criteria:

- Patients who are deteriorating;
- Patients whose situations are clinically uncertain, with limited reversibility;

Potential patient participants will be identified daily from scanning ward 'whiteboards'. As this is a feasibility study we will critically examine these criteria i.e. identifying which patients are likely to potentially benefit from the AMBER care bundle on the control wards.

On the intervention wards, patients who are eligible for the AMBER care bundle will be recruited. Patients who are being supported by the AMBER care bundle will be identified by the research nurses.

Patient exclusion criteria

Patients who do not meet any of the above criteria will not be eligible for study entry.

The clinical trial - recruitment and consent procedures for patients located on the intervention and the control wards

The objectives of the clinical trial component of this feasibility study are to:

1. To examine recruitment, retention and follow-up rates at both patient and cluster levels;

2. To test trial data collection measures and determine their optimum timing in a larger trial;

3. To provide a preliminary estimate of the effectiveness of AMBER care bundle compared with standard care to inform sample size calculation for the full trial;

4. To estimate the intra-cluster correlation coefficient and likely cluster size.

An 'active' approach will be used to identify potential participants. This requires research nurses to actively identify potential participants (patients and their relatives) rather than passively awaiting identification by the participating clinicians. Reviews of trials of palliative care services [47] and trials involving elderly people advocate an 'active recruitment' approach because of frequent problems of poor recruitment contributing to trials failing. Specifically, research nurses across the four sites, in conjunction with clinical staff, will test out identifying patients (and their relatives) on the intervention and control wards daily. On the intervention wards this comprises patients who are supported by the AMBER care bundle commenced by the clinical team using the AMBER eligibility criteria:

1. patients who are deteriorating;

2. patients whose situations are clinically uncertain, with limited reversibility;

3. patients at risk of dying during their current episode of care, despite treatment.

In the control sites only the AMBER eligibility criteria 1 and 2 are used to screen and identify potential participants.

Potential patient participants (and the close relatives of these individuals) will be identified daily from scanning ward 'whiteboards' for those who fulfil the AMBER care bundle criteria. As this is a feasibility study we will also critically examine these criteria i.e. identifying which patients are likely to potentially benefit from the AMBER care bundle.

This is a feasibility cluster randomised controlled trial, and all eligible participants admitted to a participating ward will receive the AMBER care bundle or usual care. Consent for participation is therefore for the **collection of data only**. Nonetheless, we anticipate challenges in the identification, recruitment and retention of study participants in a population at risk of fluctuating capacity.

The recruitment of patients at risk of reduced capacity

We aim to minimise the risk of this through involvement of patient groups in the development of the participant information and recruitment and consent processes. Participants will be advised they are under no obligation to take part. The purpose and intent of the work will be explained. Participants will be made aware that they can withdraw from the study at any time, with no adverse implications for their clinical care.

To comply with the MCA, research ethical approval will be obtained to seek personal consultee or nominated consultee agreement for patients with impaired capacity and for participants who lose capacity following the provision of informed consent.

Process of consent and assent for adults lacking capacity

Capacity is likely to be a major issue in this study population; the presence of confusion may reduce patients' capacity to give consent. Older people with dementia and/or cognitive impairment are considered likely to benefit from the AMBER care bundle. People with cognitive impairment the last year of life experience symptoms and care needs comparable to people with cancer [50], but have a high prevalence of poor symptom management, notably pain management and often experience aggressive treatment at the end of life [51]. The Mental Capacity Act 2005 (MCA; http://www.legislation. gov.uk/ukpga/2005/9/contents) requires that those lacking capacity are only included in research that is likely to be of direct benefit to those taking part or to benefit the particular population under study. In this study, ward patients receiving the AMBER care bundle intervention may benefit directly from improved quality of care.

Another potential direct benefit for those taking part in the study is that screening assessments for delirium on admission to the ward may identify people with delirium at an earlier stage, allowing earlier treatment. Excluding those without capacity from this research would **not** be ethical, as it would compromise the generalisability of

findings by recruitment of an unrepresentative study sample and would exclude this vulnerable group from the benefits of research evidence in improving practice.

All participants will be considered to have capacity unless established otherwise and all practicable steps are taken to enable individuals to decide for themselves if they wish to participate, for example, the Participant Information Sheet will use accessible language. A potential participant's level of capacity will be discussed with the referring clinician to identify participants with possible impaired capacity and to anticipate the likely consent procedure. Capacity will be established when meeting the individual using the **MCA four step process**:

(i) the individual is able to understand the information about the study;

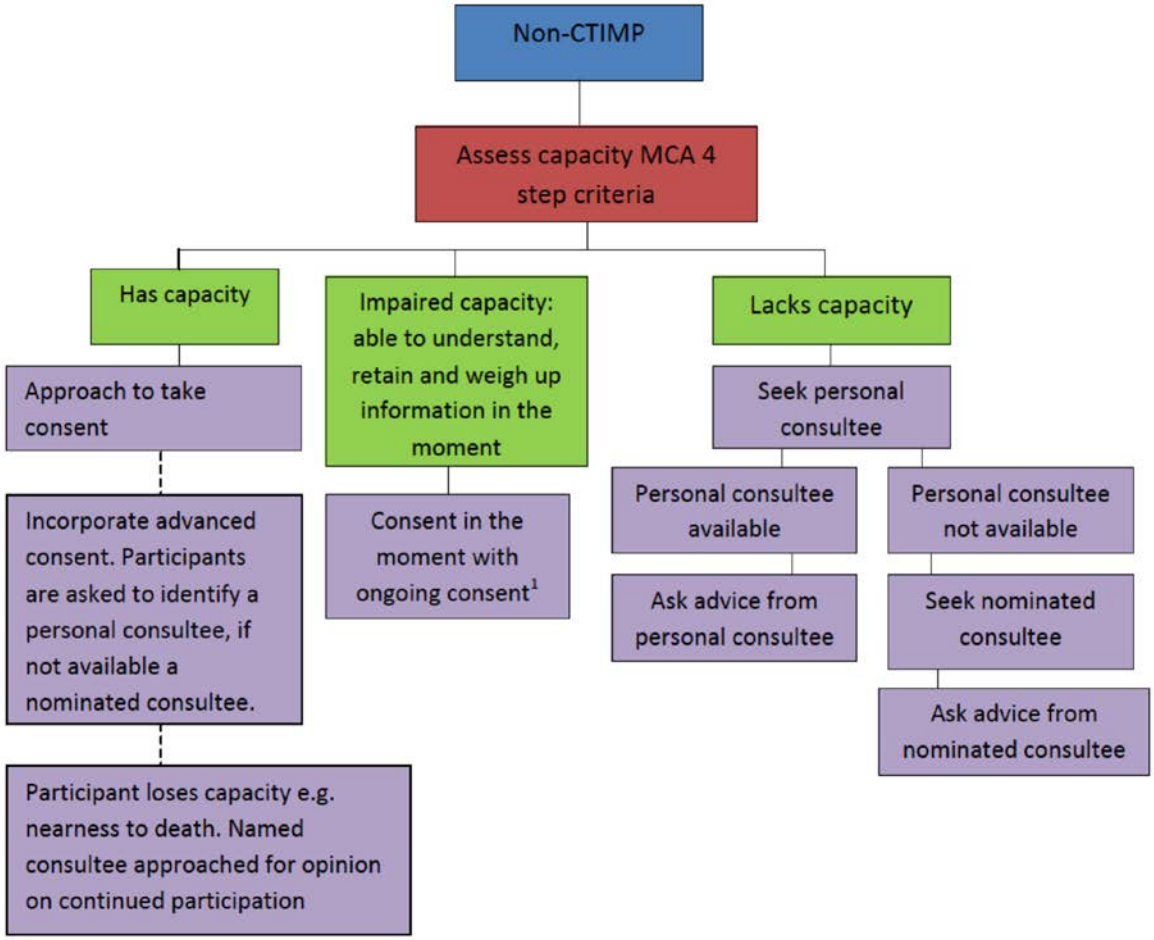
(ii) retain the information (even for a short time);

(iii) use or weigh up that information

(iv) communicate his or her decision (by any means) [52].

Potential participants' mental capacity is anticipated as ranging from able to give informed consent to lacking capacity to give informed consent (refer to figure 4 below). We have previously developed processes of consent and assent that are tailored to an individual's level of capacity that incorporate varying levels of capacity. We anticipate that some participants may lose capacity during the study because, for example, of nearness to death. Incorporating different processes of consent and assent is used in research studies on end of life care involving adults of advanced age [53-55]. This aims to enable individuals with varying levels of capacity to decide for themselves if they wish to participate, and incorporate a process of assent for adults lacking capacity.

Figure 4: Process of consent[56]



Consent in the moment for participants with impaired capacity

For adults with impaired capacity, but able to understand, retain and weigh-up information in the moment a process of consent in the moment is used with on-going consent whereby informed consent to participate is reaffirmed prior to each data collection point [57]. The approach of consent in the moment was developed and used in studies involving adults with dementia and/or cognitive impairment [57, 58]. If a participant's capacity declines that they are **no** longer able to give informed consent in the moment, the researchers follow the procedure for adults lacking capacity detailed below.

Advanced consent and assent for participants who lose capacity

An advanced consent will be incorporated in anticipation that some participants may lose capacity and may no longer have capacity to indicate their right to withdraw from the study. The process of advanced consent is informed by previous studies with older people [55] and on end of life care [59]. Participants able to give informed consent are asked to indicate should they lose capacity in the future if they would wish to continue to be involved in the study, and if they indicate yes then they are asked to nominate a

personal consultee (e.g. next of kin), or if not available a nominated or professional consultee (e.g. social worker). The named consultee is approached if in the future the participant loses capacity to an extent they are no longer able to indicate their right to withdraw from the study and to complete patient reported outcome measures, requiring instead a proxy informant (e.g. informal or formal carer). The procedure for assent for adults lacking capacity is followed to ascertain the named consultee's opinion on the individual's continued participation (see below).

Assent for adults lacking capacity

When an adult lacks capacity a personal consultee will be sought to give an opinion as to whether in his/her knowledge of the potential participant they would have wanted to participate in the study had they had capacity to indicate this, and that participation would not cause undue distress [52, 55]. A personal consultee comprises next of kin, immediate carer or attorney with Lasting Power of Attorney. Identified consultees will be given an information leaflet about the study, a letter detailing why they have been chosen as a consultee and their responsibilities as a consultee. The consultee documents are informed by our current research with older people [55], the MCA [52] and MCA guidance [60], and our PPI involvement. If contact cannot be made with a personal consultee within one week of initial identification a nominated consultee will be contacted [53, 54]. The nominated consultee will have a professional relationship with the potential participant, but cannot be connected to study e.g. a geriatrician, social worker [53]. The nominated consultee will be asked based on their knowledge of the individual to give an opinion on whether it is in the individual's best interest to participate in the study and that they would not be caused undue distress by participating. Participants' GPs will also be informed of their involvement in the study.

Documentation of study participation

All participants who provide written informed consent to participate in the study will be given a copy of the information sheet to retain and keep, and all consultees giving written assent. Participants will be offered a copy of their signed consent form to keep if they wish, and consultees a copy of their signed assent form. A copy of the signed consent/assent form will be filed in the participant's medical notes. The research team will retain the original signed consent form. For those people who give consent for their general practitioner (GP) to be informed about their participation in the study (on the consent form), the GP will be sent a copy of the consent form using the contact details provided.

DATA COLLECTION FOR THE CLINICAL TRIAL

After providing informed consent research nurses will then conduct baseline face-to-face interviews with patients located on wards that provide the AMBER care bundle and those cared for in control wards. This will permit them to collect baseline data (T1) that captures demographic and clinical circumstances e.g. co-morbidities, prescribed medication etc. They will also assess symptom burden and the 'Patient/family anxiety and communication subscale' using the I-POS and also administer the *'howRwe'* (explained below).

Testing the primary outcome measures

The first primary outcome measure we will test is the effect of the AMBER care bundle on the **'Patient/family anxiety and communication subscale' of the Integrated Palliative care Outcome Scale (I-POS)** [61, 62]. This proposed outcome is based on the overall aims of the AMBER care bundle and findings from our recent comparative observational study where psychosocial issues were shown to be important patient and family centred concerns [21]. Specifically, the 'Patient/family anxiety and communication subscale' includes being in receipt of information, addressing practical matters, sharing feelings with family, being at peace, and patients' and families levels of anxiety and depression.

A general background to the Integrated Palliative care Outcome (I-POS) measure is presented below[2]. Briefly, it comprises 17 items scored from 0 (best) to 4 (worst) and assesses physical symptoms, psychological and spiritual needs, and provision of information and support [61]. The I-POS has undergone extensive validation testing including cognitive interviewing to assess acceptability and content/face validity and to identify cognitive processing issues following the model of Tourangeau [63]. We have evidence that the IPOS is a robust, valid and reliable measure, and would provide discrimination between relevant groups (paper submitted for publication). We identified among 373 patient participants that the IPOS can discriminate well between

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[2] ***The Palliative care Outcome Scale***

The Palliative care Outcome Scale (POS) was developed in the 1990s and includes domains important to patients with advanced progressive illness [1]. It consists of 10 items scored from 0 (best) to 4 (worst). It assesses physical symptoms, psychological and spiritual needs, and provision of information and support. Following patient and clinician feedback, a symptom module (POS-S, adapted for specific conditions) was added [2-6]. Staff versions of POS and POS-S – important when the target population is so ill and frequently unable to complete patient-reported versions - are brief, user-friendly clinical outcome measures designed for health care practitioners to assess an individual's symptoms and concerns. They typically take less than 10 minutes to complete [7]. Both patient and staff versions of POS and POS-S have undergone extensive psychometric study. POS has validity and internal consistency in a variety of settings, including hospital inpatient care and community and outpatient services, hospice inpatient, day care and home care [7, 8]. Moreover, it demonstrates construct validity and re-test reliability [9], and factor analysis has identified important underlying constructs relating to psychological well-being and quality of care [10]. It shows good reliability, with consensus between staff and patients for eight out of 10 items at first assessment [7]. IPOS specifically combines the most important elements of POS and POS-S into one brief, integrated, user-friendly practical measure.

1. Hearn, J. and I.J. Higginson, *Outcome measures in palliative care for advanced cancer patients: a review.* J Public Health Med, 1997. 19(2): p. 193-9. 2. Sleeman, K.E. and I.J. Higginson, *A psychometric validation of two brief measures to assess palliative need in patients severely affected by multiple sclerosis.* J Pain Symptom Manage, 2013. 46(3): p. 406-12. 3. Saleem, T.Z., et al., *Symptom prevalence, severity and palliative care needs assessment using the Palliative Outcome Scale: a cross-sectional study of patients with Parkinson's disease and related neurological conditions.* Palliat Med, 2013. 27(8): p. 722-31. 4. Murphy, E.L., et al., *Understanding symptoms in patients with advanced chronic kidney disease managed without dialysis: use of a short patient-completed assessment tool.* Nephron Clin.Pract., 2009. 111(1): p. c74-c80. 5. Higginson, I.J., et al., *Symptom prevalence and severity in people severely affected by multiple sclerosis.* J Palliat Care, 2006. 22(3): p. 158-65. 6. Higginson, I.J., et al., *Symptoms and quality of life in late stage Parkinson syndromes: a longitudinal community study of predictive factors.* PLoS One, 2012. 7(11): p. e46327. 7. Hearn, J. and I.J. Higginson, *Development and validation of a core outcome measure for palliative care: the palliative care outcome scale. Palliative Care Core Audit Project Advisory Group.* Qual Health Care, 1999. 8(4): p. 219-27. 8. Antunes, B., et al., *Screening for depression in advanced disease: psychometric properties, sensitivity, and specificity of two items of the Palliative Care Outcome Scale (POS).* J Pain Symptom Manage, 2015. 49(2): p. 277-88. 9. Hearn, J. and I.J. Higginson, *Development and validation of a core outcome measure for palliative care: the palliative care outcome scale. Palliative Care Core Audit Project Advisory Group.* Qual.Health Care, 1999. 8(4): p. 219-227. 10. Siegert, R.J., et al., *Psychological well-being and quality of care: a factor-analytic examination of the palliative care outcome scale.* Journal of Pain and Symptom Management, 2010. 40(1): p. 67-74. 11. Tourangeau, R., *Cognitive Aspects of Survey Measurement and Mismeasurement. [References].* International Journal of Public Opinion Research, 2003. 15(1): p. 3-7.

patients with different illness and functional characteristics. For example, in the known-group comparisons (during our testing of construct validity) the total IPOS and subscale scores discriminated well between patients that were in an unstable/deteriorating phase compared to those with more stable phase of illness (F=15.0, p < 0.001 for total IPOS and F= 3.6, p<0.03 for the 'Patient/family anxiety and communication subscale').

The purpose of the feasibility study is also to examine alternative primary outcome measure [64]. We will therefore test a validated patient-reported measure **(the *'howRwe'* [65][3])** that to examine changes in patients' reported experiences of health care, highly relevant to these whose situations are clinically uncertain, and their families. A general background to the howRwe measure is presented immediately below. This measure is succinct (29 words in length) and highly accessible (readability=Flesch-Kincaid grade score 2.2). It consists of four items; two relate to the delivery of clinical care (being treated kindly, and being listened and explained to). Two further items relate to the organisation of their care, including waiting to see a health care professional (time wasted) and how well organised patients perceive the ward to be. The '*howRwe'* has been used successfully across in-patient, outpatient general practice, care homes and in domiciliary care [66] [67].

These two measures will be reassessed at follow-up points **T2 (days 3-5)** and **T3 (days 10-14)**.

Criteria for success of the primary outcomes we are testing will be judged on the following criteria [68]:

- Appropriateness: for patients with advanced illness e.g. degree of missing data;
- Reliability
- Validity: (including content validity for example how well participants' believe the measures capture what is important to them. We will use qualitative interviews to explore this issue;

[3] **The *howRwe***
In England the NHS undertakes many national surveys of patient experience. However measures are unwieldy and lengthy with many over 300 words long. The howRwe was developed the first short generic patient experience measure for use across all health and social care sectors[1]. It comprises just 29 words and includes two items relating to clinical care (treat you kindly; listen and explain) and two items relating to the organisation of care (see you promptly; well organised) as perceived by patients. Each item has four possible responses (excellent, good, fair and poor). The summary howRwe score is calculated for individual respondents by adding the scores for each item, giving a scale with 13 possible values from the floor, 0 (4 x poor) to the ceiling, 12 (4 x excellent). When reporting the results for a group comprising more than one respondent, mean scores are transformed arithmetically to a 0 to 100 scale, where 100 indicates that all respondents rated excellent and 0 that all rated poor. This allows the mean item scores to be compared with the summary howRwe score on a common scale. The measure was recently trailed among 828 older patients and has undergone extensive psychometric study [2, 3]. HowRwe has validity and internal consistency in a variety of settings, including hospital, care homes in the community. Moreover, it demonstrates good internal consistency, concurrent validity, discriminant and construct validity.

1. Benson, T. and H.W.W. Potts, *A short generic patient experience questionnaire: howRwe development and validation.* BMC Health Services Research, 2014. 14(499).
2. Benson, T., et al., *Evaluation of a new short generic measure of health status: howRU.* Informatics in Primary Care, 2010. 18: p. 89-101
3. Benson, T. and C. Bowman, *Health-Related Quality of Life and Patient Experience in Care Homes*, in *Medicine 2.0*. 2013: London,

- Responsiveness: (including the identification of floor and ceiling effects at baseline, and change between the respective time points);

- Acceptability: for patients (including reasons for non-completion through qualitative interviews, and final open question on study participation in the quantitative data collection booklet at baseline and the final time point);

- Feasibility: for example is the measure easy to administer to patients in an inpatient hospital setting.

We also want to better understand to what extent the process of providing study information seeking and obtaining consent and their study involvement in both arms of study potentially improve a patient's perceived situation and result in study contamination. We will make use of a successful strategy obtaining from a recent study we conducted to examine the effectiveness of Dignity Therapy for people living with advanced cancer [69]. Specifically, patient participants in both groups will be questioned at T2 (day 3-5) and T3 (day 10-14) to evaluate to what extent they found participating in the process of obtaining consent and the overall research process 'helpful', 'made life more meaningful', 'heightened their sense of purpose', 'lessened suffering', and 'increased their will to live'. We have observed that self-reports of the benefits of being involved in the research process were generally more positive in the intervention group than in the control [70]. However, qualitative accounts from this study, reported by participants in the control group, included statements that being involved in research meant 'somebody cared about me' and also represented 'an opportunity to talk to somebody about problems with a sympathetic and sensitive researcher' [71]. This feasibility cluster RCT will seek these views and maybe be able to inform us whether merely speaking to patients is as effective/therapeutic as, and cheaper than delivering, the intervention – this would be important to know.

THE FOLLOW-BACK QUALYCARE SURVEY

The objectives of the follow-back post bereavement survey within this feasibility study are:

1. To test trial data collection measures and determine their optimum timing in a larger trial.

2. To provide a preliminary estimate of the effectiveness of AMBER care bundle compared with standard care to inform sample size calculation for the full trial

3. To examine differences in the use of financial resources between the AMBER care bundle and standard care

Participant inclusion criteria for the follow-back QUALYCARE postal survey

Potential participants for the follow-back post bereavement survey will include the next of kin (NOK) or named relatives of deceased patients either: (i) who were in

receipt of the support from the AMBER care bundle on intervention wards, or (ii) those identified as fulfilling the AMBER care bundle criteria on control wards. We will identify the next of kin for patients who died: (i) whilst they were in-patients OR (ii) on discharge within 100 days or less.

The selection and recruitment of participants for the follow-back QUALYCARE postal survey

We wish to examine the experiences of both groups of patients during their hospital experience, also at a time when they are potentially unable to share their views, but from a different perspective. We therefore wish to collect this information from family or close friends of patients who were cared for on the intervention and control wards and who fulfilled the criteria to be supported by the AMBER care bundle. To achieve this we will use a follow-back, post bereavement survey that will be at minimum of 10-12 weeks after the death of a patient.

All identified NOK will then be sent an introduction letter from the palliative care team at each of the participating DGHs 10-12 weeks following bereavement, with the survey questionnaire and a *Royal College of Psychiatrists* bereavement support leaflet. Up to two reminders will be sent to people who have not responded at 2 and 4 weeks after the initial posting; the second reminder will include another copy of the questionnaire.

Upon receipt of a completed questionnaire (see below), the research team will record arrival into the spreadsheet, check completion, and levels of distress and grief intensity. A follow-up telephone interview (of about 15 minutes) may also take place, although this is entirely optional, and only if participants write in the questionnaire they agree and provide their contact details. This telephone interview aims to clarify information if appropriate (e.g. answers which appear to be accidentally missing) and to talk about the questionnaire, so the researcher can ascertain the impact and effect of the questionnaire on the participant (to screen for distress and serious concerns).

Redacted/anonymised completed survey questionnaires will then be locked in a cabinet in a locked office in the team's department. Access to the data is restricted and controlled. If there is need for clarifications regarding the questionnaire or follow-up to assess the impact of the questionnaire on the participant and potential distress, and provided the participant has agreed to be contacted and provided contact details, a member of the research team makes contact to arrange a telephone interview.

Data collection for the follow-back survey

We will use a modified version of the **QUALYCARE postal survey** [72] which is highly acceptable to participants in bereavement research [73]. This survey instrument examines the last 1-2 months of the decedent's life, including quality and consistency of information and communication with clinicians.

Specifically, it comprises four brief and robust measurement tools previously used in cancer and end-of-life care studies. These tools collect information on health and social care services use and informal care (Client Service Receipt Inventory - CSRI) [74,

75], patient palliative outcomes in the week prior to death (Integrated Palliative Outcome Scale [I-POS]) [61, 62] health-related quality of life (EuroQoL EQ-5D)] [76], and respondents' bereavement outcomes (Texas Revised Inventory of Grief - TRIG) [77]. Further questions explore preferences for (and actual) place of death, relevant local issues and socio-demographic and clinical data. The format and navigation of the questionnaire have been refined according to cognitive theory literature [78]. Further, the QUALYCARE questionnaire has been piloted and improved to enhance acceptability among 20 bereaved relatives, recruited via the palliative medicine department of a London hospital [73].

THE QUALITATIVE COMPONENT

The qualitative component of this feasibility study includes interviews with patients, their relative or close friends, non-participant observation of the multidisciplinary team (MDT) meetings and focus groups with health care professionals. The specific objectives of these components of work are:

1. To examine the extent to which the AMBER care bundle requires further refinement or adaptation (for example referral criteria to identify which patients would benefit most) to suit local conditions;

2. To assess the acceptability of the AMBER care bundle to patients, their families and health care professionals;

3. To determine the active ingredients of the AMBER care bundle that need to be maintained to ensure fidelity of the intervention for a full trial;

4. To assess compliance and barriers to the delivery of the AMBER care bundle;

Participant inclusion criteria for the qualitative interviews

Potential participants on the control wards will include:

1. Patients who are deteriorating;

2. Patients whose situations are clinically uncertain, with limited reversibility;

3. Relative or close friends of the above.

4. Patients or relatives who are able to meet face to face or have the interview over the phone telephone

Potential participants on the intervention wards will include:

1. Patients who were supported by the AMBER care bundle

2. Relative or close friends of those patients.

3. Patients or relatives who are able to meet face to face or have the interview over the phone telephone

Exclusion criteria for the qualitative interviews:

Our exclusion criteria for this component of the study will comprise:

1. Patients who do not meet the criteria above;

2. Patients who are not able to provide informed consent due to capacity-related issues;

3. Patients considered by ward staff to be too unwell to interview and/or too distressed to approach;

4. Any relatives/close friends, who are not willing to provide informed consent;

5. Relative/close relatives considered by ward staff to be too distressed to approach;

Procedure for recruitment for the qualitative interviews with patients on the intervention and control wards

The research nurses will:

(i) Identify up to 20 patients (5 per ward) known to be deteriorating, clinically unstable with limited reversibility, and at risk of dying during their episode of care on the intervention and control wards.

(ii) Will discuss these potential patient participants with their clinical team to assess if appropriate prior to approaching the patient. They will also be selected according to pre-agreed criteria (range of age groups, gender, disease type, ethnic group). If deemed to be appropriate the research nurse will ask if they would be willing to be interviewed by the trained researcher. All patients will be provided with a comprehensive study information sheet explaining the nature of the study and their potential involvement. This document will not allude to therapeutic promises. Nor will they allude to unacceptable inducement or refer to any coercion for not participating. If in agreement, the researcher will contact the potential participants no less than 24 hours later to address any questions or concerns that they might have and to establish their decision to take part in the study or not. . Due to challenging nature of patient's clinical situation, interviews will take place over the phone, if the potential participant is not able to meet face-to-face. A mutually convenient time will be arranged to conduct the interview. The researcher will once again explain the study in full and then obtain their informed consent should they wish to share their time and views on care. The interview will commence after informed

consent has been obtained either in writing in a face-to-face interview, or verbally recorded in a telephone interview. A potential participant will be given an information sheet regarding the interview by the research nurse and in give informed to be contacted by the researcher regarding the interview. Understanding on what taking part will be discussed by the researcher with the potential participant over the telephone again as part of the informed consent process. Verbal consent will be documented by the researcher on the consent form for telephone interviews, and the respective researcher will sign and date. A copy of the signed consent form will be sent/emailed to the participant after the interview pending their preference. Any recordings or notes during the telephone call will be destroyed immediately if the participant decides not to take part, or withdraw at any point during the interview.

Procedure for recruitment for the qualitative interviews with relatives or close friends of patients on the intervention and control wards

The research nurses will be asked to:

(i) Identify up to 20 family members or close friends (5 per ward) of patients known to be deteriorating, clinically unstable with limited reversibility patients known to be deteriorating, clinically unstable with limited reversibility, and at risk of dying during their episode of care on the intervention and control wards,

(ii) Approach potential participants (family members or close friends (according to pre-agreed criteria to reflect a range of age groups, gender, disease type, ethnic group) while they are visiting their dependants, and ask if they would be willing to be interviewed by the trained researcher. All family members or close friends) will be provided with a comprehensive study information sheet explaining the nature of the study and their potential involvement. This document will not allude to therapeutic promises. Nor will they allude to unacceptable inducement or refer to any coercion for not participating. If in agreement, the researcher will contact the potential participants no less than 24 hours later to address any questions or concerns that they might have and to establish their decision to take part in the study or not. A mutually convenient time will be arranged to conduct the interview offering either a face-to-face interview or a telephone interview if a face-to-face interview is not convenient. The researcher will once again explain the study in full and then obtain their written informed consent should they wish to share their time and views on care. The interview will commence after informed consent has been obtained either in writing in a face-to-face interview, or verbally recorded in a telephone interview. Even though, the potential participant will be given an information sheet by the research nurses regarding the interview prior to the interview, the content of the information sheet will be covered over the phone again. Verbal consent process will be recorded on the consent form for telephone interviews and this consent form will be sent/emailed to the participant after the interview. Any recordings or notes during the telephone

call will be destroyed immediately if the participant decide not to consent, or withdraw at any point during the interview.

Data collection for the qualitative interviews with patients and relatives or close friends

The interview topic guide aim to explore patients' and their relative/close friends' insights into the delivery of care and their perception of involvement in critical decisions regarding their care and treatment whilst in hospital. Interviews will be recorded on an encrypted voice recorder. During transcription, all potential identifiable information will be anonymised. Once transcripts are anonymised and coded appropriately, recordings will be destroyed.

Non-participant observation of the MDTs and focus groups with staff members

Prior to the meeting taking place the researcher will obtain written informed consent from MDT members who wish to have their views and behaviours observed and then recorded in field notes. We are, however, mindful that some health care professionals may arrive late from other meetings or as a result of their clinical commitments, or pop in and out as required. We wish for the consent process to be minimally intrusive on the group setting as possible so as to not affect natural behaviour and to be as practical as is possible. We will make a note of those who turn up late and obtain their retrospective consent (should they wish to offer this).

Health care professionals will also be invited if they wish to participate in a ward based multi-professional focus group to explore their views to caring for patients whose situations are clinically uncertain, views about the AMBER care bundle (if on the intervention wards), and views regarding the feasibility cluster RCT. The focus groups will be organised during lunch times to optimise participation and will be catered with food and refreshments to offset any inconvenience staff many experience. Participants will be asked to give an informed consent on arrival at the venue for the focus group. The researcher will take the consent

Data collection for the non-participant observation and focus groups

On the two wards designated as intervention wards we will make notes of who is present at the meetings (i.e. professional groups), frequency of the meetings, the length and type of conversations relating to patients identified as fulfilling the criteria for the AMBER care bundle. We will specifically note who (which professions) contribute to conversations, what specific actions are discussed that relate to their care, and how decision-making processes are developed including the management of end of life issues. We will also observe if there is a leader and champions emerging between MDT members, and trust, respect and value placed on each professional within the team. We will conduct similar observations on the two control wards with prior knowledge from the research nurses of patients who fulfil the AMBER care bundle criteria. Observations will be written down as field notes immediately after leaving the meeting. ALL field notes that relate to conversations about individual patients and their families will be devoid of any identifying characteristics.

The topic guide for their focus group with health care professionals located on the AMBER care bundle (intervention) and those located on control wards will explore their views on the delivery of care and patient and family centre outcomes in wards with and without AMBER. More specifically, we are interested to understand their insights into the ways in which the AMBER care bundle influences communication with patients and their family members or close friends; improves their confidence, competence and empowerment of working with patients with advanced disease; facilitates improved team working; and explore what changes may be required to enhance its operation. We will also explore their view on the manner in which the trial has been organised. Some of the observations from these meetings and focus groups will be incorporated with the measure of 'standard' or 'usual' care.

The 'standard' or 'usual' care questionnaire

The questionnaire aims to capture what standard care comprises for patients with clinically uncertain outcomes and their families. The format and navigation of the questionnaire have been refined based on expert opinions including members of the Project Advisory Group and senior clinical colleagues. Further, we discussed the 'standard' or 'usual' care questionnaire with the multidisciplinary team members of three wards of a London hospital to improve capture of the key components of standard care and to enhance acceptability, for example, clarity of language.

Prior to completing the questionnaire, the researcher/research nurse will obtain written informed consent from the healthcare professionals including a consultant, ward sister/manager, a junior doctor, a healthcare assistant and a staff nurse who work on the study ward. We will ask several healthcare professionals, rather than one representative per ward, in order to have a broader understanding of standard care. The questionnaire asks about 'standard' care for patients when uncertainty surrounds their clinical outcomes, and their families. Questions encompass initial care planning and general practices (e.g. advance care planning), recognising dying, referral and discharge procedures. The questionnaire takes 10 to 20 minutes to complete pending amount of textual data provided. We will ask staff to complete questionnaire at three time points comprising: 1) baseline (prior to implementation of the AMBER care bundle for the intervention wards); 2) mid-patient recruitment (6 weeks after the recruitment of the first participant); and 3) at the end of the patient recruitment. We are mindful that some of the procedures at the ward might not change drastically throughout the study, especially at the comparison sites. Hence why, at mid-patient recruitment and end of patient recruitment time points, we are giving the option of only answering the questions, where there has been a change in the procedure since the previous time point.

The case note review and 'heat maps'

In addition to the 'standard' or 'usual' care questionnaire, the nurse educator will complete an audit tool developed by the AMBER care bundle developers as part of the quality improvement process. This audit tool is routinely used in over 30 hospitals internationally including England, Wales, and Australia. The incorporation of the audit

tool data aims to enhance our understanding of 'standard' or 'usual' care at ward level and how this might change overtime. The audit tool comprises a standardised format for case note review of hospital patient records and a 'heat map' on patient mortality over a one-year year period.

The case note review follows the standard quality improvement procedures to implement the AMBER care bundle. The case note review will be completed retrospectively and involve at least 20 patients per ward, purposively selected comprising 10 patients who died in the hospital and 10 patients who were discharged and died within 100 days of discharge. The case note review will be conducted at the end of the feasibility trial for the comparison wards and prior to implementation of the AMBER care bundle at the intervention wards. In the intervention wards, these processes are part of the routine quality improvement processes of the AMBER care bundle. All identifiable patient information will be removed and anonymised. Anonymised data then will be shared with the research team.

AMBER readiness

The case note reviews conducted at the intervention wards after the implementation of the AMBER care bundle will also assess 'the AMBER readiness' of the ward. The AMBER readiness criteria assesses whether the AMBER care bundle was implemented to an acceptable standard and whether this standard was sustained during the trial. The clinical educator responsible from implementing the intervention will decide whether the AMBER care bundle is implemented correctly by checking against the criteria below.

1. 80% staff received the training programme
2. 5 staff randomly selected can correctly describe AMBER Care Bundle four key components
3. Staff identify patients eligible for AMBER Care Bundle without prompting in e.g. ward rounds
4. Staff discuss clinical uncertainty and care preferences with patients supported by AMBER Care Bundle, and with families
5. Senior staff discuss 'what is important to the patient' and the clinical escalation plan in e.g. staff handovers
6. AMBER Care Bundle documented in patient records, and discharge letters detail escalation plan and preferences for care.

While data required for the 1st to 5th criteria will be derived from clinical educator's observations during time spent on the ward, data required for the 6th criteria will be extracted from the case note reviews. All identifiable patient information will be removed and anonymised. Anonymised data then will be shared with the research

team.

A 'heat map' aims to identify the rate of patient mortality over a one-year period at hospital and ward level as part of the quality improvement process. The quality improvement data will inform contextual understanding on similarities/differences in mortality between the hospital sites and understanding on heterogeneity in terms of patient deaths between the clusters. The heat maps will provide contextual information at ward level on the number of deaths during admission, and up to a 100 days after admission. For example, the information regarding the number of patients who died with individualised approach to last days of life care, and number of readmissions before a patient's death will inform us about the standard care procedures. This will enable comparison between the intervention and control wards on for example, place of death. The heat map will be produced by the informatics department for each study site. A census date will be agreed on, in order to ensure that the data assessed at all study sites are covering the same time period. Each hospital and wards within will be given unique identification numbers. Anonymous data will be shared with the research team. 'Heat maps' will also be shared with the hospital staff and the study wads, which will inform them about the suitability of the wards for the AMBER care bundle and enable them to use this data for quality assessment. Heat maps will not include any identifiable patient related information.

QUANTITATIVE ANALYSIS

Data management and security

All personal data will be managed according to the principles established in the Data Protection Act 1998. All of the researchers will undertake and update GCP training, and current research governance processes will be followed. Completed demographic forms, questionnaires and interview transcripts will be anonymised using a unique study identification number and contain no patient identifiable data. The participant identification number and linkage with the participant's name only occurs on the consent form and codebook. The codebook is held in a password protected Excel Spread sheet, stored on an encrypted memory stick at KCL in a locked filing cabinet. Questionnaires, demographics forms and transcripts will be stored separately to the consent forms, each in a separate locked cabinet.

Data entry

All data will be entered into a pre-designed SPSS database. Data entry is continuously monitored through supervision meetings where a set of rules develops and exceptions will be discussed. Ten percent of the data will be double entered and cross checks will be conducted to identify the percentage of items with discordances, missing data and systematic errors (percentage of double-checked data will be adjusted according to outcome of cross-checks).

Sample size for the feasibility cluster RCT

Because this is a feasibility study, a formal power calculation is not appropriate, as effectiveness is not being evaluated. Any investigations of changes in study parameters

are exploratory only. The results generated from this study will be used to inform the power calculation for a possible definitive study [79] [80]. However, based on available data that approximately 11-19 patients die on these wards per month, we estimate that over the period of the feasibility study we will be able to recruit 40-45 patients in each arm. This will provide us with important information to fulfil the key objectives concerned with understanding how best to recruit, examine study participant retention, and the feasibility and acceptability of the overall trial.

We will undertake analysis according to CONSORT guidelines in collaboration with our Clinical Trials Unit; the statistician being blind to the intervention. A flow chart will be developed to present the follow-up rate for each group (intervention and control wards) with the reasons for non-completion of the primary outcome.

1. To assess the feasibility of recruiting participants, the numbers of patients who are screened, are eligible, are assessed for AMBER care bundle, have capacity to consent, consent to data collection will be summarised.

2. Missing data will be examined ascertaining cause(s) of missing data, and the impact of this missing data on the results (last value carried forward, next value carried backward, and mean value) [81, 82].

3. Differences between participants and non-participants will be examined to ascertain potential sample bias.

4. Parametric and non-parametric statistical methods (depending on the distribution of the data) will be used to describe and compare changes in the I-POS symptom scores on the 'Patient/family anxiety and communication subscale' (changes in being in receipt of information, addressing practical matters, sharing feelings with family, being at peace, and patients' and families' levels of anxiety and depression) between baseline and time points one and two. If appropriate, bivariate analysis (and if necessary and sufficient power, multivariable regression analysis) is used to identify and explore the factors associated with the outcome variables.

5. The data analysis in the economic evaluation will examine resource implications from both a (i) health/social care and (ii) societal perspective. We will make preliminary cost-effectiveness calculations (e.g. combining CSRI data on costs and EQ-5D score). Economic evaluation is an emergent area in palliative care and uncertainty surrounds best practice [75]. The feasibility study will test procedures to inform the economic evaluation in the full cluster RCT protocol.

QUALITATIVE DATA ANALYSIS

The qualitative data analysis approach is informed by the framework approach to inductively code and organise the data, and identify emerging themes from the interviews [83]. We are very experienced in using framework as an approach to qualitative data analysis. It is an approach widely used in palliative care and health

services research [84] [85] [86]. Framework involves a five stage matrix-based approach comprising:

(i) **Familiarisation:** We will immerse ourselves in the raw data from the interviews by listening in detail to audio recordings, reading and rereading transcripts, and also studying field notes to list key ideas and recurrent themes;

(ii) **Identifying a thematic framework:** We will then develop and thematic framework to identify all the key issues, concepts, and themes so the data can be examined. This will be carried out by drawing on a priori issues and questions derived from the aims and objectives of the study as well as issues raised by the participants themselves. The end product of this stage will comprise a detailed 'index' of the data so we can 'label' the data into manageable chunks for subsequent retrieval and exploration;

(iii) **Indexing:** We will apply our thematic framework to all the data in textual form by annotating the transcripts with numerical codes from the index, usually supported by short text descriptors to elaborate the index heading. We will make use of NVivo data analysis software to facilitate this process.

(iv) **Charting:** We will rearrange the data according to the appropriate part of the thematic framework to which they relate and form charts. The charting process involves a considerable amount of abstraction and synthesis;

(v) **Mapping and interpretation:** Last, we will make use of the charts to define concepts, map the range and nature of phenomena, create typologies and find associations between themes with a view to providing explanations for the findings.

We will address issues of rigour and trustworthiness in the analysis. We (JK and CE) will randomly select interview transcripts to review the application of the thematic framework, coding, and completeness of the framework. Where coding differs or areas of the framework are inconsistent, these issues will be reconsidered until a consensus is achieved [87]. During this process, we will take care to examine what appear to be more unusual views and ask what the data tells us about their causes to avoid making unwarranted claims about patterns and regularities in the data [87]. Excerpts from the interview transcripts will be presented to illustrate themes and will represent a range of views rather than relying on selected individuals. We may make made some use of numerical and verbal counting as this can help clarify patterns emerging from the data while recognising that the main emphasis is to identify meanings and conceptual categories [88] .

INTEGRATION OF THE DATA SETS

The aim of the data integration is to examine different aspects of AMBER care bundle experience and participation in the research study. Data will be integrated using a

method of data 'triangulation' which combines data sources from more than one source (quantitative and qualitative) to address the same phenomenon [89] [90].

The process of triangulating findings from the different methodological approaches will take place at the interpretation stage of a feasibility study after all data sets have been analysed separately. Specifically, we will list the findings from each component of a study and then consider where findings from each approach agree (convergence), offer complementary information on the same issue (complementarity), or appear to contradict each other (discrepancy or dissonance). We will be looking for instances of convergence but also for disagreements between findings from different approaches. We believe that disagreement is not a sign that something necessarily went wrong with our feasibility study. Indeed, instances of "inter-method discrepancy" may lead to a better understanding of how the AMBER care bundle operates, its effects, and where it can be improved. We will also look for instances of silence - where a theme or finding arises from one data set but not others. Silence might be expected because of the strengths of different methods to examine different aspects of the AMBER care bundle. We may also encounter 'surprise silences' that help us to increase our understanding of anomalies and inconsistencies, and potential variations in effects across sites, reasons for success or failure of the AMBER care bundle in different contexts, and barriers and facilitators to achieve benefit and sustainability.

DISSEMINATION STRATEGY

Outputs for this feasibility cluster RCT of the AMBER care bundle versus standard care pertain to the methodology for a full RCT and a model of identifying and serving clinical uncertainty at the end of life. A negative feasibility trial will help redirect services. This study will also act as a springboard for research on palliative interventions for patients whose situations are clinically uncertain in hospital settings. Findings will disseminated through:

1. International conference presentations on the feasibility of implementing in practice and likely patient benefit; and the feasibility of conducting a cluster RCT of the AMBER care bundle in hospital settings;

2. We also aim to publish the findings of our feasibility study in open access high impact online journals, and will prepare (with support from our patient collaborators) user friendly summaries for patients and users to access, as well as on patient advice and support forums (e.g. patient.co.uk, BBC health), and well as to national patient and carer groups. For this we will also work with patient groups in individual centres, and national and international charities.

3. We will develop web pages about the project on our own website - www.csi.kcl.ac.uk with links to other relevant organisations, encouraging those organisations to link with us. These will be updated regularly with information on study progress, newsletters etc. The project team will also take advantage of social media forums such as Twitter, blogs, podcasts, and other media sites to disseminate these findings further. Linking to other projects within the Cicely

Saunders Institute at KCL we will explore opportunities to develop e-based education/training packages for clinicians and others, based on the findings of the research.

PATIENT AND PUBLIC INVOLVEMENT

This study was discussed extensively with our PPI group that includes patients (pts), pt reps and current/former carers of pts with advanced illness. They expressed profound concern about end of life care in hospitals and wish to see change. The outcomes of these discussions have influenced the focus of our study objectives, research questions, and our planned methods for the proposed feasibility cluster RCT. Two PPI members, Colleen Ewart and Sylvia Bailey reviewed the lay summary to ensure that it is comprehensible and appropriate. They have agreed to assist us to critically review the applicability of the survey tools, proposed outcomes, the content and wording of research ethics documentation, the conduct of the feasibility study, the interpretation of data and dissemination of study findings. They also agreed to support our work in developing a grant application for a definitive cluster RCT. We will reimburse travel expenses and pay an hourly fee in recognition of their time/contribution in accordance with NIHR Involvement guidance.

ETHICAL REQUIREMENTS AND ETHICAL CONSIDERATIONS

Ethics and Health Research Authority (HRA)

The sponsor will ensure that the trial protocol, participant information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate research ethics committee and HRA, prior to any participant recruitment. The protocol, all other supporting documents including and agreed amendments, will be documented and submitted for ethical and regulatory approval as required. Amendments will not be implemented prior to receipt of the required approval(s).

Before any NHS site may be opened to recruit participants, the Chief Investigator/Principal Investigator or designee must ensure confirmation of Capacity and Capability has been given by the local R&D office. It is the responsibility of the CI/ PI or designee at each site to ensure that all subsequent amendments gain the necessary approvals.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The chief investigator will prepare the APR.

Within 90 days after the end of the trial, the CI/Sponsor will ensure that the main REC is notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with a summary report of the trial, which will then be submitted to the REC within 1 year after the end of the trial.

Ethical considerations pertaining to this feasibility cluster RCT

The feasibility cluster RCT comprises several inter-connected components each of which bring with them unique ethical considerations that warrant attention.

ALL INDIVIDUALS WHO ARE APPROACHED TO PARTICIPATE IN THE STUDY WILL BE REQUIRED TO FULLY COMPREHEND ALL THE BENEFITS, RISKS AND BURDENS OF THEIR INVOLVEMENT IN THE RESEARCH AND PROVIDE WRITTEN INFORMED CONSENT TO THIS EFFECT BEFORE DATA COLLECTION IS PERMITTED TO COMMENCE

The feasibility cluster RCT

The feasibility cluster RCT will field test the procedures and develop the methodology for a full cluster RCT to examine AMBER care bundle versus usual care raises a number of important ethical issues. Importantly, this is a study of the trial; ALL eligible participants admitted to a participating ward will receive the AMBER care bundle or continue to receive usual care on the control wards. Consent for participation in the trial is therefore for the collection of data only. Nonetheless, we anticipate some ethical challenges in the identification, recruitment and retention of study participants in a population at risk of fluctuating mental capacity. We aim to minimise any risks to participants through involvement of our patient and public involvement (PPI) group in the development of the participant information and recruitment and consent processes.

The main ethical issue for the clinical trial are the processes of seeking consent and assent for adults with impaired capacity/ lacking capacity. Adults lacking capacity are likely to experience the most complex needs and greatest benefit from the intervention. The NRES toolkit on research involving adults lacking capacity guides the study [91]. A process of assent is used with adults lacking capacity following procedures in the Mental Capacity Act 2005, and research studies [92]. A process of on-going consent is used with adults with impaired capacity to enable them to consent in the moment with continual monitoring of verbal/non-verbal signs to stop. A process of advanced consent is incorporated for older people able to give informed consent, but who may lose capacity over the course of the study e.g. nearness to death [59]. This ensures an individual's right to withdraw at any stage is upheld if they lose capacity to be able to indicate this. Applicants Evans and Koffman are experienced in research involving adults lacking capacity; both Koffman and Evans have recently worked on a study on capacity and consent in research on palliative and end of life care, funded by Marie-Curie Cancer Care UK (http://www.csi.kcl.ac.uk/mcc.html).

(i) The post bereavement study

This study will make particular use of bereaved relatives' accounts of care of their loved one/dependants in the last 1-2 months of life. It is now widely accepted that post-bereavement research is ethical and feasible, particularly in light of research findings showing benefits as perceived by research participants [93] [94] [95]

New evidence [73] suggests that although engaging in follow-back surveys can evoke some degree of distress, many participants, nevertheless, still report it to be a positive experience. We therefore believe it would be unethical *not* to undertake a study that enables relatives to express their views about the quality of care received by the patients and has therefore the potential to lead to improvements in care and benefits to others (particularly as altruism has been found to be a main reason for patients and carers to participate in end of life research).

Using postal surveys of bereaved relatives is now a very well established and accepted method of research in end of life care, with tradition in the UK [72] [96] [97]. It is indeed the approach recommended in the recent End of Life Care Strategy (Department of Health 2008). We are, however, conscious of the ethical challenges and committed to minimising the risks of harm and maximising the benefits for potential participants.

The research nurses in collaboration with the clinical team located on each of the four wards in each of the four hospital sites will identify eligible bereaved relatives from their death registration records. They will write to them on behalf of the research study team, inviting them to take part in the study. The invitation letter has been carefully drafted and included with this is an information leaflet which gives further assurance by describing the procedure in more detail. A postal approach to recruitment respects participants' privacy and gives them ample freedom to consider taking part in the study. In case they agree, it offers opportunity for participants to revisit consent after completing the questionnaire, by deciding whether or not to return it. Carers will be contacted NO EARLIER than THREE months following bereavement to minimise any distress and potential harm.

The acceptability of our research approach was recently examined in detail [73] and observed a higher response to the postal questionnaire (11/17) in comparison to the face-to-face interviews (9/16). Eleven people completed the postal questionnaire of which half (n=6) did not want to be further contacted to talk about it. This finding suggests that a postal approach might be most comfortable for the participants. However, although using a postal approach respects privacy and avoids bias in responses through presence of a researcher, it also reduces opportunity for screening for distress and supporting the participants as need be. We have therefore considered with great care, procedures to minimise distress and will inform ALL potential participants about sources of support (by providing all with a leaflet on bereavement produced by the Royal College of Psychiatrists). We have also included other measures to deal with participant's distress and serious concerns.

We propose to use an "opt out" rather than "opt in" approach to recruiting the participants; this has also been successfully used in our recent study [98] and in previous national and local studies, and across different ethnic groups [96] [97].

The decision has followed extensive debate with experts in ethics, end of life care and bereavement research and clinicians, consultation of national guidance and analysis of

previous studies on the matter. Although an "opt in" approach is deemed ethically more defensible, we believe it poses a number of scientific problems that seriously threaten the scientific rigour of the research produced. These have been documented in robust studies that have been reviewed by the National Research Ethics Service (Information sheets & consent forms – Guidance for reviewers and researchers version 3.5 May 2009). An RCT conducted in the UK showed response rates of 38% using "opt in" vs. 50% using "opt out" and several differences between the participants recruited in the two groups [99]. Other studies support these findings and show that the use of "opt in" approaches have resulted in the past in biased samples (with potential for inequity in research participation) and reduced response rates to levels that studies are not generalisable to their populations and lead to erroneous conclusions. Moreover, no evidence exists to show that an "opt out" approach for initial contact is in any way harmful. In fact, some argue that opting out is more personal and adequate in societies and research areas where the majority is willing to participate in research. The willingness to participate and benefits to participants in end of life care research, support the fact that the majority will welcome the opportunity to participate and derive more benefit than distress. Scientifically, a low response rate will reduce the sample size in our study – this is important as we are aiming to achieve a representative sample.

We will use a now widely used questionnaire [72] which has been adapted so as to ONLY include the sections relevant to this feasibility cluster RCT [21]. The original questionnaire integrates robust measures, has been carefully piloted and improved. A psychometric validation study showed encouraging results on the reliability and discriminatory power of many of the questions [100]. This provides further reassurance of the appropriateness of the methods proposed.

Several end-of-life care studies and our recent cross-sectional observational study [21] provide cogent evidence that many bereaved relatives indeed welcome the opportunity to make a contribution towards improving care for others by taking part in research of this nature. It has also been shown that this kind of study can be carried out in an ethical manner. In our feasibility cluster RCT, bereaved relatives as well as health and social care professionals will have the important opportunity to contribute towards improving end of life care in the future, and this has been shown to be beneficial.

(ii) The qualitative interviews and focus groups:

We wish to conduct face-to-face and over the telephone, semi-structured interviews among patients, family member or close friends, and focus groups with health and social care professionals to explore their views on the delivery and outcomes in wards with and without the AMBER Care Bundle, and views on the study design. In the first instance, we hope to identify some patients who fulfil the criteria to be supported by the AMBER care bundle on the intervention, as well as patients who fulfil the same study criteria, but who are located on the control wards. We also wish to interview a small number of family members (or close friends) of these patients to explore their perspectives on involvement in care decisions. We hope this will allow us to explore

the 'real-time' patient and family (and close friends) experiences of care on the two types of ward. To this end, we have considerable experience in conducting interviews among patients living with and dying from advanced disease and also family members [21]. We are conscious of the vulnerability they may experience at this critical time in their lives, and yet we have identified despite this a willingness and enthusiasm to engage in research of this type [101] .

We are very aware and very sensitive to the possibility that questions in the interviews, as well as the invitation letter and questionnaire may bring to light unhappy memories and experiences to potential participants. The research team's considerable experience and sensitized skills in the conduct of end of life care studies and interviewing patients towards the end of life, their carers and bereaved relatives, together with training and clinical experience in palliative medicine and health psychology, provide reassurance that all information giving and interviewing will be conducted sensitively; any distress (potential or real) will be identified and handled appropriately.

(iii) Non-participant observation of multi-disciplinary team meetings (MDTs)

It has been suggested that fully informed written consent can be impractical when conducting non-participant observation; the process of explaining the purpose of the researchers' presence can cause people to change their behaviours which distorts findings [102]. We will, nevertheless, obtain written informed consent from MDT members (prior to meetings taking place) who wish to have their views and behaviours observed and then recorded in field notes. We are, however, mindful that some health care professionals may arrive late from other meetings or as a result of their clinical commitments, or pop in and out as required. We wish for the consent process to be minimally intrusive on the group setting as possible so as to not affect natural behaviours, and to be as practical as is possible. We will make a note of those who turn up late and obtain their retrospective consent (should they wish to offer this). All relevant observations will be written down as field notes immediately after leaving the meeting. Field notes that relate to conversations about individual patients and their families will be devoid of any identifying characteristics.

(iv) 'Standard' or 'Usual' Care Questionnaire

We will be obtaining written informed consent prior to completion of the questionnaire baseline and confirmed verbally at each time point. Each participant will be assigned an individual identification number. If data is reported indicating requirement for follow-up, for example, staff distress or patient safety concerns, this is discussed with the participant and appropriate action agree, for example, escalation to senior ward staff.

(v) Case note review and 'heat maps'

Case note review and 'heat maps' will not include any patient identifiable information. The clinical educator will review the information collected and discuss with the respective senior clinical leads in accordance with standard procedures for the quality

improvement processes for the AMBER care bundle. A unique identification number will be used for each site and all study data will be de-identified.

INSURANCE

Data transfer and storage

All interviews will be recorded using an encrypted digital audio recorder; the device has a password protected access and live AES256 encryption (most robust encryption format available). All transcripts will be pseudo- anonymised, and quotations will only be used in such a way as to preserve the anonymity of study participants. Audio recording of the face-to-face interviews will only take place with the expressed permission of the participant. An ID codebook will be used to assign ID numbers to participants for the purposes of data entry and transcription. This codebook will be stored digitally in an encrypted file separately from the consent forms, information sheets and demographic data. Transcribers will sign a confidentiality agreement and type up only anonymous information.

ALL personal data stored as manual files by the research team (including audio recordings) will be kept secure in locked cabinets in a locked office at the Department of Palliative Care, Policy & Rehabilitation, King's College London, in accordance with the requirements of the Data Protection Act and the Department Data Management Guidelines. Access will be restricted and controlled. ALL personal data as digital files by the research team will be stored and encrypted on university computers at the Department of Palliative Care, Policy & Rehabilitation, King's College London, in accordance with the requirements of the Data Protection Act and the Department Data management Guidelines. Again, access will be restricted and controlled, and only anonymised data will be transferred by electronic media. Data will be only transferred electronically via NHS mail (which is encrypted) and the original consent forms will be transferred via post.

Record keeping and archiving

At the end of the study all essential documentation will be archived securely by the CI for a minimum of 7 years from the declaration of end of trial.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with all applicable regulatory requirements.

The sponsor will notify sites when trial documentation can be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

MANAGEMENT AND GOVERNANCE OF THIS STUDY

Expertise and experience

The project applicants form an expert panel who will meet three –four monthly over the course of the study to oversee the project and contribute to: the project development; the execution and analysis of the post-bereavement survey; the intervention development and theoretical modelling; the feasibility of the intervention and testing procedures; and the final data synthesis to develop the methodology for a full RCT and inform a model of integrated working between specialists and generalist nurses.

The expert panel comprises individuals with the breadth and depth of expertise required to undertake the study. Expertise include: developing and evaluating complex interventions (Koffman, Evans & Murtagh), palliative care service development and provision (Koffman, Evans, Murtagh & Barclay), managing large postal surveys (Koffman & Evans), statistical analysis (Wei), qualitative analysis (Koffman & Evans) and health economics (Yi).

The expert panel (the co-applicants) have responsibility for progress and delivery of outputs, and oversee the research team on a day-to-day basis, with strategic programme direction from the Project Advisory Group (through 4 monthly meetings, and advise between meetings, as required), and the Lay Project Advisory Group meeting 4-6 monthly on specific aspects of the study.

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