PROTOCOL

The clinical and cost effectiveness of CBT plus treatment as usual for the treatment of depression in advanced cancer: a randomised controlled trial (CanTalk)

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Synopsis of Study

Depression is a prevalent mental disorder in patients with cancer, which negatively impacts on the patient and the carer. It reduces quality of life, reduces adherence rates to medications, prolongs hospital admissions, increases healthcare costs, and is an indicator of early death. Cognitive Behaviour Therapy (CBT) is an empirically effective treatment for major depression and its use compares favourably with antidepressant treatments and has been shown to be associated with significant therapeutic gains over time. There is little evidence on the efficacy of CBT in advanced cancer patients.

We shall recruit patients throughout the UK with advanced cancer no longer amenable to curative treatment and assess for presence of depression. Those with depression will be entered in to the study and, through a randomised controlled trial; we shall assess the clinical and cost effectiveness of cognitive behavioural therapy.

RESEARCH OBJECTIVES

Hypothesis

Cognitive Behaviour Therapy plus treatment as usual is more clinically and cost effective than treatment as usual for major depression in adults with cancer that is no longer amenable to curative treatment.

Primary objective

To determine through a randomised controlled trial the clinical effectiveness of Cognitive Behaviour Therapy plus treatment as usual compared to treatment as usual for depression in adults with cancer which is no longer amenable to curative treatment.

Secondary objective

To determine through a randomised controlled trial the cost effectiveness of Cognitive Behavioural Therapy plus treatment as usual compared to treatment as usual for depression in adults with cancer which is no longer amenable to curative treatment.

Existing Research

Depression is one of the most prevalent mental disorders in patients with cancer (McDaniel, 1995). It worsens the quality of life for patients and their carers (Alexander et al, 1993), may reduce adherence with medication, is a psychological burden on carers, and may prolong hospitalisation and increase healthcare costs (Bowers and Boyle, 2003). Untreated depression is also an independent predictor of early death in patients with advanced cancer (Lloyd –Williams et al, 2009).

Screening, diagnosis and prevalence of depression in cancer patients

Psychological disturbance in advanced cancer may be difficult to diagnose. A poor prognosis in cancer is often associated with significant anxiety and some sadness appropriate to the challenges that are presented by the illness. Diagnosing and measuring depression in advanced cancer is complex because depression, which should be treated (Pessin et al, 2005), may be discounted or confused with common psychological and physical symptoms (e.g. anorexia, lethargy) associated with cancer (Price and Hotopf, 2009). In advanced cancer the prevalence of depressive symptoms, measured using structured clinical interviews, ranges from 5% to 45% (Hotopf et al, 2002; Potash and Breitbart, 2002) and may vary with the type of cancer (Massie, 2004). Although the HTA brief suggests that rates of major depression in this population are 38%, we consider that this is the highest likely estimate. When the most stringent criteria are used, approximately 5-15% of patients will meet a diagnosis of major depression (Potash and Breitbart, 2002). In the only study examining depression in advanced cancer in primary care prevalence rates of just over 4% were generated (Reeve et al, 2007). This is much lower than the rates of 8-18% expected in a GP population (King et al, 2008). However, patients in the Reeve et al (2007) study were identified from registers of people with advanced metastatic cancer receiving only palliative treatment. Our examination of general practice data suggests that less than 10% of all cancer patients are placed on palliative care registers, even though 60% of cancer patients may have advanced disease (more data is presented in the feasibility section). Secondly, identifying patients from palliative care registers approaches a restricted population; for example only the sickest patients may be placed on such registers and may have been too ill to respond to the authors survey. Thirdly, the psychological and psychiatric morbidity associated with cancer goes undetected and undertreated in over 80% of people (Wilson et al, 2000; Maguire, 1985). Given these varied data, for the purposes of our study, we shall assume a more conservative prevalence rate for major depression in advanced cancer patients: 15% in oncology outpatients and 10% in General Practice patients. Using these estimates will enhance the feasibility of the trial.

A prevalence rate of 38% for major depressive disorder is quoted in the commissioning brief, but this estimate is possibly too optimistic. We have chosen lower prevalence rates of major depressive disorder of 15% for patients in oncology clinics and 10% for patients recruited from primary care. Thus more people will need to be screened to achieve the numbers required. We have extensive experience of successfully recruiting cancer patients and conducting research in a primary care setting and believe these conservative estimates are justified.

The European Association for Palliative Care calls for screening and treatment of depression in terminal cancer (Stiefel et al, 2001). A number of different methods are used to screen for depression and distress (Thekkumpurath et al, 2008). Two simple questions (Arroll et al, 2003) are

the simplest way and has been shown to exclude depression (97% negative predictive value) in non depressed individuals in cancer and palliative care (Mitchell, 2008; Low et al, 2009). The first two questions, known as the Patient Health Questionnaire-2 (Kroenke et al, 2003), of the 9 item Patient Health Questionnaire (Kroenke et al, 2002), are routinely used in screening for depression in primary care. Such screening is acceptable if it is followed by a clinical interview to confirm the clinical diagnosis of depression (Pessin et al, 2005). The MINI (Sheehan et al, 1998) provides a brief and reliable method of diagnosing depression according to DSM-IV and ICD-10 criteria in cancer patients (Sheehan et al, 1998; Passik et al, 2001, 2000, 2002; Manzanera et al, 2003; Drabe et al, 2008; Sukegawa et al, 2008; Gandubert et al, 2009; Zwahlen et al, 2008). It has been validated against the SCID (Sheenan et al, 1995), DSM-IIIR and the CIDI (Amorim et al, 1998).

Recruitment of patients with advanced cancer

Difficulties in recruitment and follow-up due to associated mental and physical exhaustion present major hurdles to conducting research in a palliative care population and there may be high rates of attrition due to early death (Jordhøy et al, 1999). Health professionals may also be protective towards patients by discouraging them from making the extra effort needed for research. For example, between 9-19% of all those approached agreed to participate in a trial of CBT for depression in advanced cancer (Moorey et al, 2009; Savard et al, 2006; Edelman et al 1999). Follow-up as low as 44% at 10 weeks has been reported in severely ill palliative care patients (Moorey et al, 2009), however higher rates are possible and in some studies 75% follow-up at 3 months has been documented (Savard et al, 2006; Edelman et al, 1999). Research conducted by our research team, within the London cancer networks, has achieved follow-up rates of at least 65% in previous studies (King 2008, 2009). Furthermore, in our trials to evaluate CBT in older people with depression (Serfaty et al, 2009), CBT in cancer patients (Serfaty et al, ToT study, in preparation for publication) and advanced care planning discussions in cancer (Harrington et al, 2009), we achieved follow-up rates of over 85%. In these studies, we were able both to offer treatment at home and telephone interview follow-ups which significantly minimised attrition. Telephone CBT has been shown to be feasible and clinically and cost-effective (Simon et al, 2004; 2007). We shall therefore offer telephone CBT and follow-up for those who are unable to continue to attend in a primary care setting.

Psychological treatments used for advanced cancer

There is little evidence guiding the management of depressive symptoms in advanced cancer (Osborn et al, 2006; Williams and Dale, 2006; Newell et al, 2002). Although a recent study suggests that an intervention delivered by a cancer nurse may be beneficial (Strong et al, 2008), this model requires a specialist service and has not been tested in advanced disease. Cognitive Behaviour Therapy (CBT) is an empirically effective treatment for major depression and its use compares favourably with antidepressant treatments and has been shown to be associated with significant therapeutic gains over time. It is an approach that may be pertinent to treating a population who may experience significant symptom burden from advanced cancer and palliative treatments, such as nausea and pain. For depression in advanced cancer, CBT approaches appear the most promising (Price and Hotopf, 2009). Two Cochrane reviews of psychosocial treatments in advanced cancer have been published. Findings from these treatments are conflicting (Akechi et al, 2009; Edwards et al, 2009). In the meta-analysis of psychotherapy for depression in advanced cancer by Akechi et al

(2009), all of which used the Profile Of Mood States (POMS) as an outcome measure, heterogeneous results were generated. Six studies were cited; 4 used supportive psychotherapy (Goodwin et al, 2001; Linn et al, 1982; Spiegel et al, 1981; Wood et al, 1997), one group CBT (Edelman, 1999) and one problem solving (Classen et al, 2001). Akechi, et al, (2009) conclude that there is a "need for more well designed trials of cognitive behavioural therapy on depression in patients with advanced cancer." Edwards et al (2009) identified five well designed studies using psychological interventions for depression in women with metastatic breast cancer (Cunningham, 1998; Edelman 1999; Goodwin et al, 2001; Koopman et al, 1998; Spiegel et al, 1989). However only the first two suggested a short term benefit on the POMS from the use of CBT. The effects were lost at 6 month follow-up, possibly because group therapy did not sufficiently address the needs of specific individuals (Edwards et al, 2009).

Individualized rather than group CBT is likely to facilitate recruitment and minimise attrition. It has been preferred by patients with head and neck cancer (Osborn et al, 2006; Semple et al, 2005) and benefits were reported in a recent study of CBT for depression in women with metastatic breast cancer (Savard et al, 2006). The application of individualised CBT has been further developed for use in palliative care populations using the model developed by Moorey et al (1989; 1994; 1996) and adapted by Mannix (co-applicants). This approach modifies a standard CBT model by ensuring that physical, psychological, emotional, spiritual and existential issues in the context of cancer are all addressed. CBT can be delivered by training either established therapists or other healthcare professionals to deliver CBT in advanced cancer or palliative care. We recently conducted a pilot study, using trained CBT therapists, to compare the use of this specialised approach with aromatherapy for the treatment of psychological distress at all stages of cancer (Serfaty et al, in preparation for publication). Although small numbers (n=39) were involved, recruitment proceeded well and a trend towards a beneficial outcome with CBT was found. In a pilot study by Mannix et al (2006), a range of palliative care professionals were trained to use cognitive therapy skills in everyday practice. Though this was helpful with anxiety, there did not appear to be an effect on depression (Moorey et al, 2009). Levels of training and expertise in CBT are known to affect outcome in people with depressive disorder. Given the complex nature of depression in advanced cancer patients, we therefore advocate that CBT for depression should only delivered by experienced CBT therapists who have been trained to adapt their skills to treat cancer patients. This is also consistent with level 4 interventions suggested by NICE for people with cancer who have psychological distress and with delivery of services in the modern NHS.

Finally, patients with advanced cancer may not always be able to attend for therapy sessions because of physical problems associated with their illness. CBT delivered over the telephone may not only be clinically helpful but more importantly help engage patients offered treatment for depression in primary care (Simon et al, 2004, 2009). As far as we know, this model has never been applied to patients with cancer.

The economic analysis of interventions must be considered given that a cost reduction of 20% has been associated with psychological interventions (Chiles et al, 1999). Although economic analyses in psycho-oncology are scarce (Carlson et al, 2004) with equivocal evidence for lower utilisation of health care resources in cancer (Rosenberg et al, 2002; Simpson et al, 2001) and metastatic breast cancer (Lemieux et al, 2006), there is a case for ensuring economic analyses are undertaken (Carlson et al, 2004).

In conclusion, patients with advanced cancer may be difficult to recruit and retain in trials and therefore multiple recruitment methods and a flexible approach to minimise attrition are necessary. As suggested in the brief, diagnostic procedures need to be defined. Most well designed trials to date in advanced cancer have focussed only on breast cancer patients with metastatic disease and treatment of those with all types of advanced cancer needs further work. CBT interventions have tended to use group CBT approaches, though individualised CBT may be preferred by patients and have sustained effects. Our group has extensive experience in the treatment of training therapists in CBT to treat those with advanced cancer. The best hope of a longer term benefit for CBT for depression is offered if the intervention is delivered by an experienced therapist. The use of telephone CBT, known to be effective in depressed primary care patients, would facilitate ongoing access for those who may not always be able to attend for therapy. We shall conduct a (randomised controlled) trial using experienced therapists to evaluate whether the addition of CBT to treatment as usual (TAU) brings about a greater improvement in depression, and saves costs, when compared to TAU alone.

METHODS:

Design

A parallel group single blind randomised controlled trial. Patients will be randomised using the resources of PRIMENT, a Clinical Research Centre (CRC) registered clinical trials unit.

Location

Multiple recruitment methods will maximise accrual to the trial and the 6 month follow up period will minimize attrition due to deteriorating health or early death. Patients will be recruited from:

- Specialist oncology outpatient services in three London cancer networks

  North Central London Cancer Network: University College Hospital, Royal Free Hospital, *Marie Curie Hospice Hampstead* (Camden IAPT), the Whittington Hospital (Haringey IAPT) and the North Middlesex Hospital (Haringey IAPT).

  North East London Cancer network: Homerton Hospital and St Bartholomew's Hospital, London Hospital (*Hackney and City IAPT*), and Newham Hospital (Newham IAPT).

  South East London Cancer Network: Kings College Hospital, *Lewisham University Hospital* (Lewisham IAPT), *St Thomas' Hospital* (*Lambeth IAPT*) and *Guy's Hospital* (Southwark IAPT).

- Primary care using GP cancer/palliative care registers through the NIHR Primary Care Research Network (PCRN)

  GP practices that form part of the PCRN Primary Care Research Network in areas in which co-applicants are based and where IAPT services are well established across the UK including London, North West England (Knowsley IAPT) and North East England (South Tyneside IAPT). Recruitment will be facilitated by PCRN staff, and National Cancer Research Network (NCRN) staff. Patients will be identified from GP held cancer and palliative care registers and checked for suitability with local practice staff. Thus we shall be able to provide data on recruitment

patterns from primary care in areas other than London and also confirm that the model of care can be delivered across the UK.

(*we are awaiting written confirmation for sites listed in italics*)

CBT will be delivered by Improving Access to Psychological Therapies (IAPT) therapists who will have received additional training in CBT skills for patients with advanced cancer (Moorey and Mannix). IAPT centres are being rolled out across England and will be characteristic of NHS service provision available. Trial participants will have depression and other complex needs and individual CBT will be used. We have selected areas where IAPT centres are well established which will enable delivery of CBT to the intervention group promptly once recruitment has commenced.

Target Population

People aged ≥18 with cancer of all types, including haematological malignancies, will be identified from those whom clinicians confirm have cancer no longer amenable to cure and are aware of their diagnosis and likely prognosis will be screened for depression using two questions (Low et al, 2009). Those scoring positively will proceed to a more in depth assessment for eligibility (MINI interview). We have added the Patient Health Questionnaire (PHQ-9; Kroenke et al, 2002), a valid measure of the depression routinely used in a General Practice setting.

Entry criteria

Inclusion criteria:

- A diagnosis of cancer not amenable to curative treatment (this includes patients initially diagnosed with metastatic disease, those at first or subsequent incurable recurrence and who may be receiving palliative treatments including non-curative radiotherapy, chemotherapy biological therapy or surgery) verified by contacting GPs or oncologist.
- A clinical diagnosis of depression through clinical interview on the MINI (Sheenan et al, 1998).
- Agreement to be randomised.
- Sufficient understanding of English to be able to engage in CBT.
- The patient is eligible for IAPT - either they or their GP is in an appropriate catchment area.
- Agreement for GP to be involved so that referral to IAPT can take place through GP.

Exclusion criteria:

- Clinician estimated survival of less than 4 months (verified by contacting patients' oncologists/GP).
- Suicidal intent rated as high using the MINI at initial assessment.
- Currently receiving or having received a psychological intervention recommended by NICE aimed at treating depression (e.g. Interpersonal Psychotherapy, CBT etc) in the last 2 months.
- Suspected alcohol dependence using the Alcohol Use disorders Identification Test (AUDIT; Saunders et al, 1993).

Process of Recruitment
From outpatient oncology clinics:

This study will form part of the NCRN clinical trials portfolio. NCRN support staff will facilitate recruitment in oncology outpatient clinics. Support staff will be asked to check patients' addresses to determine that they are eligible to be referred to an IAPT therapist. Support staff will screen suitable patients for depression using the two question tool. Patients who score positive will be provided with an information pack and asked if they would be willing to see a researcher who will answer any questions and assess them for the study. Those who score positive but do not wish to participate will be asked if they are agreeable for us to inform their GP or oncology team that they may be depressed. Those who score positive and agree in principle to participate will then be seen by the researcher who will undertake a further assessment (MINI interview to diagnose DSM IV depression) and obtain written consent for participation in the study. The researcher will collect baseline assessment measures and then liaise with PRIMENT clinical trials unit where a person independent of the researcher will randomise the patients, inform them into which group they have been allocated and also make a referral to IAPT. Each patient's GP will be notified into which trial arm their patient has been allocated.

From GP lists, the PCRN Primary Care Research Network staff

We will identify suitable patients from data bases and then contact people by phone or face to face in practices to see whether they are willing to answer the two screening questions for depression. The PCRN staff will use similar recruitment procedures as those described above.

Self-referral

Posters and leaflets will be placed in approved oncology and GP sites with information about the study. The leaflet contains the PHQ-2 for a quick assessment on mood. If they screen positive, they can either (a) approach the clinical team within the site or (b) contact Input from Clinical Trials Unit directly using the reply slip attached to the leaflet. The process of recruitment will be similar to those detailed above

Feasibility phase

We plan to build an assessment of feasibility into the study. This phase will be conducted in the London cancer networks and the research team has already successfully recruited to previous large scale studies in palliative care (Walsh et al, 2007; King et al, 2008, 2009). Although we are confident that recruitment is feasible, our steering group will monitor recruitment and ensure that the patient numbers are being achieved and that the intervention is deliverable by IAPT therapists. This will be done by reviewing the progress of the trial at 6 months into recruitment (end of year 1).

As part of the feasibility phase, during the orientation period, we shall work with IAPT to ensure each IAPT therapist involved gains experience and confidence with at least two patients with advanced cancer prior to applying their skills to patients recruited to the trial. We have already liaised with a number of IAPT and oncology centres and include written agreements indicating participation. We also have provision for further centres to be involved if necessary.

Randomisation

Randomisation to either TAU or TAU plus CBT will take place after patients have been assessed for suitability, consented to the trial and baseline measures have been collected. This will be conducted by PRIMENT CTU using a web based system. Antidepressants are a predictor of outcome (Kamboj et al, 2005). However, in cancer tricyclic antidepressants may be preferentially prescribed over SSRIs because they may be helpful in the management of pain and are less associated with nausea and gastrointestinal problems which may exacerbate the physical symptoms of cancer and the side effects of chemotherapy. Determining the therapeutic dose of antidepressant is complex and even low doses of tricyclic antidepressants may be effective (Furukawa et al, 2002). We cannot stipulate that post randomisation SSRIs cannot be used or that the dose should be fixed. Withholding a recognised treatment for depression would be unethical, particularly in the treatment as usual group. Moreover, this would not reflect treatment as usual. We will therefore stratify people according to whether they are prescribed an antidepressant or not. We will conduct a post hoc analysis to confirm that randomisation was balanced in both groups with respect to antidepressant dose by standardising prescribed antidepressants into equivalent doses of imipramine (Serfaty et al, 2009). This will be done by recording all antidepressants prescribed (name dose and frequency prescribed) during the trial. This will include SSRIs and other antidepressants such as tricyclics which are often used in small doses for symptom control in end of life care. We will convert antidepressant dose for any drug into a mean equivalent dose of imipramine following a method we used in another trial of CBT for depressed older people in primary care (Serfaty et al, 2009). This will enable us to confirm that doses of all antidepressants are similar in both groups.

Our experience in our trial of CBT for depressed older people, many of whom had physical problems, was that the doses of antidepressants were balanced between the 3 intervention groups and that the number of people starting an antidepressant was extremely small (4 out of 204 people by 10 month follow-up-Serfaty al, 2009).

Masking

It will not be possible for patients or therapists to remain blind to the treatment group. The researchers and PCRN assessors will be blinded and will be asked to guess group allocation at 3 months and 6 months post baseline. Unmasking will not occur until databases are closed.

CONSENT AND ETHICAL ISSUES:

Obtaining informed consent from participants

All the information leaflets and consent forms will be adhered to and have been agreed by the relevant NRES committee. Consent will be a two stage process. We will indicate to patients that we wish to screen for low mood to determine whether they may be suitable for a further study (as described above). We will confirm if they screen positive for possible depression they give us permission to contact their oncology team/GP and that we will need written consent for this. Those who screen positive will then be offered more information about the study in the form of a detailed pack. The patients will be offered an appointment for further assessment, to take place no less than

48 hours later to give the patient chance to read the material. It will be emphasised that they do not have to attend and should cancel the appointment if, on reading the material, they decide not to participate. If they meet inclusion criteria, written informed consent will be obtained prior to randomisation into the study.

Ethical Arrangements

Approval of the National Research Ethics Service (NRES) has been obtained. As this is a vulnerable group, and patients may tire easily, interviews are kept short. All patients will benefit by their GPs being made aware of depression which is often missed. IAPT therapists are experienced in assessing suicide risk and will be able to direct/refer patients to appropriate care pathways if necessary. Our previous work in cancer patients suggests that CBT is well received, of potential benefit and does no harm. Patients' travel costs for research sessions will be met by the project funding. An expert Trial Steering Group will monitor the progress of the study according to UCL research governance procedures.

We have also establish a Data Monitoring and Ethics Committee that will meet at least annually to monitor data collection and report and adverse events. IAPT therapists will access their usual supervision procedures. Regular clinical supervision mechanisms are in already in place in the host academic department in UCL to support field researchers working with people with advanced progressive and life threatening conditions.

Risks and anticipated benefits for trial participants and society

As with any comparative treatment trial which includes a treatment as usual arm, participants may desire an active psychological treatment for depression, but this is to be restricted in the TAU group. It remains to be determined whether psychological treatments are of benefit in this population and it is not ethical in the longer term to provide an intervention which may not be effective and by virtue of its costs restricts access to other potentially beneficial interventions. There is no evidence to suggest that CBT is harmful. IAPT therapists are experienced at conducting risk assessment. Where continued participation would be inappropriate, such as development of suicidal intent requiring inpatient admission, participants will be withdrawn from the study.

All participants will however benefit from being identified as depressed and with their permission their managing clinical team will be notified of their participation in the trial. This is consistent with level 3 interventions under the National Institute of Clinical Excellence (2004) guidelines for good practice. The potential benefits of the trial are that it will reduce distress and improve quality of life in participants and carers.

There may be an increase in direct costs to society, but it is hoped that the improved level of functioning will reduce the indirect costs to society as a whole. The findings from the study will also inform the evidence base and clinical guideline for people with advanced cancer internationally. All health professionals delivering interventions will follow risk assessment procedures and will follow the sites' Trust policies for managing risk.

For the qualitative component of the study ('CanTalk study: your experience of CBT'), we anticipate no risk to participants. Although participants may find a topic sensitive or upsetting, research

suggests that participants may find talking about such topics therapeutic (Hutchinson, Wilson and Skodol Wilson, 1994). We hope the qualitative component will also provide us with feedback to inform the intervention.

Informing potential trial participants of possible benefits and known risks

Trial participants will be told that we are screening for potential depression and that if positive a further assessment to determine their suitability for a trial would be necessary. Those agreeable will be given information about the trial. For those who agree to screening but who do not wish a further assessment meeting, permission will be sought to notify their clinical team that they may have depression. Those who wish further information will then be offered an appointment with a researcher who will provide them with verbal and written information according to current guidelines provided by the National Research Ethics Service (NRES). The project will be approved by the relevant ethics committee prior to the study commencing. It will be stressed to participants that they would be free to withdraw from the study at any time and this will not affect their usual care. All participants will be given at least 48 hours to think about whether they wish to participate in the trial.

Proposed time period of retention of relevant trial documentation

All data will be stored for a minimum of 10 years after the end of final analysis of the study and will be accessed by the trial statistician and chief investigator. All paper records will be stored in locked storage facilities. Personal identifiable demographic information will be kept separately from outcome measures. All electronic records will be password protected.

Proposed action to comply with 'The Medicines for Human Use (Clinical Trials) Regulations 2004'

This is not applicable as it is not a drug trial.

MEASURES:

Demographic and related data

Baseline information will be collected on age, gender, ethnicity, marital status, occupation of the main salaried person in the household before retirement, education, number of previous episodes of depression, duration of current depressive symptoms, diagnosis of cancer and when diagnosed.

Main outcome measure

- Beck Depression Inventory-II (BDI-II; Beck and Steer, 1996)
  This is a 21 item self report measure with a maximum score of 63 indicating severe depressive symptoms. It contains few items measuring affective-somatic symptoms, with 15 of the 21 items assessing negative cognitions, a target of cognitive interventions. Its psychometric properties are similar to the BDI (Beck et al, 1961), the most widely used self report instrument for measuring depressive symptoms and which has also been used in trials of psychotherapy for patients with advanced cancer (McLean et al 2008; Savard et al, 2006;

Laidlaw et al, 2005). We elected not to use the Profile of Mood States (McNair, 1992) which is often used to measure mood in psychological treatments in advanced cancer (Akechi et al 2009) and metastatic breast cancer (Edwards et al, 2009), because it is less sensitive and precise in assessing depressive symptoms and cognitive change when compared to measures solely designed for those purposes (Nezu et al, 2000). The BDI-II also has a number of cognitive elements which are particularly useful for measuring change with CBT. Other rating scales for depression have fewer cognitive elements and scales such as the PHQ-9 have not been used in this sample population and so it would not be possible to generate a suitable power analysis.

Secondary outcome measures

- Patient Health Questionnaire (PHQ9; Kroenke et al, 2002)
  This screens for depression and is used by IAPT therapists and in primary care. It is a valid measure of severity of depression in primary care (Spitzer et al, 1999; Kroenke et al, 2001) and has the advantage that it can be administered over the telephone (Pinto-Meza et al, 2005).
- EuroQol (EQ5D; Brooks, 1996; EuroQol Group, 1990)
  A generic utility measure of quality of life consisting of 5-domains and a visual analogue scale. It will be used in cost-effectiveness analysis.
- Satisfaction with care
  Collected using a visual analogue scale (scored 0 to 10 towards higher satisfaction). This method was used in our previous work (King et al, 2008).
- Eastern Cooperative Oncology Group-Performance Status (ECOG-PS; Oken et al, 1982)
  A scale to measure physical functioning based on five levels: 0, asymptomatic normal activity; 1, symptomatic but fully ambulatory; 2, symptomatic and in bed less than 50% of time; 3, symptomatic and in bed more than 50% of time; 4, 100% restricted to bed.

Measures of service utilisation

- Client Service Receipt Inventory (CSRI; Beecham and Knapp, 1992).
  We shall use a short modified version of this measure of service use which collects data directly from patients and their GP. This will replicate an approach we used in our ToT study (Serfaty et al, in preparation for publication).

Measures to reduce bias

- *Antidepressant prescribing*: We will record the name and dose, and any changes, of antidepressant prescribed during the course of the study and convert the doses prescribed into equivalent doses of imipramine using similar methods to those in our previous study (Serfaty et al, 2009) to confirm that the doses prescribed in both trial arms are equivalent.
- *Other psychological therapies*. We will make a record of any psychological intervention reported by patients or recorded in their case notes during the period of the trial.

At baseline*:*

- *Expectations at baseline*: (Borkovec, Nau, 1972) Participants will be asked to predict the degree to which they think they will improve or not on a 7 point Likert scale ranging from -3 to +3.
- *Treatment preference*: Patients' preferences for treatment will be collected on a four point Likert scale (0-3) as in Serfaty et al, (2009).

Post intervention (3 months post baseline)*:*

- *DNA rates*: Reason for not attending therapy sessions (e.g. did not like therapy, recorded death).
- *Patient satisfaction*: we shall ask participants to rate on a 5 point scale (ranging from not at all to very much) whether they found CBT useful.

At Follow up (6 months post baseline):

- *Assessment of blindness*: the researcher undertaking assessments will be asked to guess the patient's trial arm (CBT plus TAU, TAU, don't know).
- *Attrition*: Reason for missing follow-up data (e.g. too ill, died).

Timing and dynamic methods of data collection

A summary of the timing of data collection at the different time-points is shown on the table below and also on the flow chart (Fig 2). There will be two data collection points for all outcome measures, 12 and 24 weeks post baseline. Plus there will be two additional data collection points at 6 and 18 weeks for the main outcome measure, the Beck Depression Inventory-II (BDI-II), only. This will allow maximal inclusion of data from patients who die early. The BDI-II takes 10 minutes to complete which should not be too stressful for patients. Data will therefore be collected at baseline and at 6, 12, 18 and 24 weeks. Face to face contact or telephone interviews, where necessary, will be used to minimise attrition. For people recruited from oncology clinics the researchers will collect baseline information and post intervention and follow-up data will be collected by researchers from UCL and NCRN staff. For people referred from GP's UCL researchers and PCRN staff will collect baseline information and all post intervention and follow up data. A flow chart is also given (page 18).

Face to face contact between patients and researchers is our preferred choice for data collection. A variety of other dynamic methods to maximise data collection from people will be used where face to face contact may be compromised; for example if patients feel too ill or fatigued to meet for an interview. This approach includes: (i) Interviews over the telephone, where accuracy of data collection is not compromised (Simon et al 2004; 2009). (ii) Providing patients with stamped self addressed envelopes to return questionnaires with prompts by telephone. (iii) For patients with a mobile phone, if they feel it would be helpful, we will send a text message just before they are due to have a follow up reminding them to complete the outcome measure (iv) Participants who are familiar with computers and have access to one will be offered the opportunity to complete questionnaires on-line using www.surveymonkey.com or will be offered the opportunity to download the questionnaire or email the response. There is increasing knowledge of how to use computers. Even though a number of our sample population may be older people, in 2007 as many as 30% older people were accessing the net (Dutton and Helsper 2007).

Measures	T_3 Baseline	T_4 (6 wks)	T_5 (12 wks) Post intervention	T_6 (18 wks) Follow-up	T_7 (24 wks) Follow-up
PHQ-9	✓		✓		✓
BDI-II	✓	✓	✓	✓	✓
EQ5-D	✓		✓		✓
Satisfaction with care			✓		
ECOG-PS	✓		✓		✓
CSRI	✓		✓		✓
Antidepressant	✓		✓		✓
Expectation of therapy	✓				
Blindness			✓		✓
Attrition			✓		✓

We will also determine the benefits of treatment over a patient's lifetime. Extending the length of the trial is associated with problems of increased attrition and costs. We will use assumption-based modelling techniques for example Markov Modelling (Drummond et al, 2005), to explore the cost-effectiveness of the intervention using a lifetime horizon. Threshold analysis may be used as one method of framing assumptions around transition probabilities for example, in order to assess the key thresholds at which the intervention would remain cost-effective. The reliability of the model will depend on the data quality and extent of missing data from the trial.

THE INTERVENTION:

Cognitive Behaviour Therapy (in addition to Treatment As Usual):

The availability of trained psychologists to deliver psychological interventions, such as CBT, to oncology patients in secondary care settings is limited. It is possible to train palliative care practitioners in CBT skills (Mannix et al, 2006), but this does not translate into improved outcomes for depression (Moorey et al, 2009). The Government is developing a roll out programme in a community setting which aims at "improving access to psychological therapies" (IAPT). These Primary Care Trust funded IAPT centres train, supervise and supply therapists (who come from core professions in nursing, social sciences and psychology) to treat people in primary care with mental health problems. In this study, we propose to train experienced therapists to adapt their skills for treating depression in advanced cancer patients. An overview of the structure and content of sessions (to be manualised), the therapists' experience necessary, the further training which will be offered and how adherence and evaluation of therapy will be undertaken is provided as follows:

Structure of CBT sessions

16-20 sessions are recommended by NICE for severe depression in secondary care. However, our experience has been that in a primary care setting (Serfaty et, al 2009; Ward et al, 2000) considerably fewer sessions are taken up in practice. Our patients will have difficulty in coping with longer therapy given their physical limitations. Our intervention will therefore consist of up to 12 sessions of individual CBT delivered face to face or on the telephone over 3 months. Methods developed by Moorey, Mannix (co-applicant) and Serfaty (2008) in which therapists, typical of NHS practice, adapt their work to patients with advanced cancer will be used and the frequency of sessions will be flexible. We anticipate that twice weekly sessions will be offered for the first 2 weeks, weekly sessions for weeks 3 to 9 and then 2 sessions within weeks 10-12. Although we will aim to offer CBT face to face, telephone CBT is already informally used by IAPT therapists. Mannix and Moorey will teach CBT therapists how to adapt their CBT techniques for telephone counselling using similar methods to Tutty et al, (2000). All patients receiving CBT will be encouraged to complete at least 3 sessions of face to face CBT before being eligible for telephone CBT.

Content of therapy sessions

IAPT recommends that patients with moderate to severe depression and complex needs receive high intensity (step 3) work. This is consistent with level 4 psychological interventions recommended by NICE (2004) for people with cancer. The CBT intervention will use the following approach:

Session 1: assessment of problems, psycho-education about depressive disorder, introduction to the cognitive model.

Session 2: establishment of the thought-feeling link, identifying unhelpful thinking styles using specific examples from recent events.

Sessions 3 and 4; reinforcement of cognitive model, activity scheduling, behavioural experiments to test out beliefs. Adaptations of CBT for use in cancer with exploration of patients' beliefs about the negative effects of cancer and their perception of themselves in the context of their illness.

Sessions 5-10 will use standard techniques described by Beck (Beck et al, 1979) although techniques which address underlying beliefs ("schema focussed therapy") (Beck and Freeman, 1990) will be used in the latter therapy sessions.

Sessions 11-and 12: relapse prevention by helping identification of warning signs of depression, how to seek further help and how to address beliefs about termination of therapy.

We will also specifically ensure that sessions cover specified components from a checklist which include:

(i) The effects of physical illness: the impact of the illness, beliefs and expectations about the illness, their plans and hopes for care as the disease advances.

(ii) The emotional impact of the disease and coping strategies: the relationship between emotions, physical symptoms and disability caused by the disease and concerns about the patients ability to cope, their loss of control, and preparedness to accept help and discuss issues around dying.

(iii) The social impact: impact of disease and mood on behaviour and ability to fulfil roles, impact of disease on loved ones.

(iv) Spiritual and existential issues: discussion of the meaning of the illness (why me?; it's not fair schema), suicide/euthanasia issues, the potential for spiritual reconciliations, absolutions forgiveness and acceptance of unfinished business.

Telephone CBT

Recent evidence suggests that the use of telephone CBT in the treatment of depression is both clinically and cost effective (Simon et al, 2004; 2009). We will therefore use this approach where necessary with people who may not be able to continue to attend for face to face CBT. We anticipate that this situation may arise for some people whose physical condition deteriorates as their cancer progresses. This will improve engagement and minimise attrition.

Therapist experience and characteristics

All therapists, grade 7 or more, will be required to have completed a postgraduate diploma in CBT and have at least 2 years clinical experience post CBT qualification. High intensity IAPT therapists will be familiar with using one and usually two approaches; Beckian CT and/or the Seattle Behavioural Activation Programme. Our model will use the Beckian approach. However, therapists may not be familiar with the complex needs and existential issues of advanced cancer patients and they will be trained to adapt their skills to treat advanced cancer patients.

Additional training for therapists to deliver CBT for patients with advanced cancer

Therapists participating in the trial will be required to attend a two day training programme on how to apply their CBT to advanced cancer patients. The components included in the training will be developed in the orientation phase by Mannix and Moorey. A number of the components have already been used for training other healthcare professionals to deliver CBT in advanced cancer or palliative care (Moorey et al, 2009) and also to guide treatment in our previous Talk or Touch study (Serfaty et al, Talk or Touch study in preparation). We will develop a manual in the orientation phase, detailing the skills to be used. IAPT programme organisers have indicated that they are very keen to collaborate with our research (see supporting evidence) as we will train a small number of their cohort of therapists to gain the necessary skills to treat this patient group and this can then be a model of care incorporated into the IAPT programme nationally.

Quality control: Adherence to treatment and evaluation of therapy

We will use our checklist, piloted in the Talk or Touch study (Serfaty et al; in preparation for publication), to ensure that, where appropriate, physical, psychological, emotional, spiritual and existential issues have been addressed. A random sample of 1 in 10 audiotapes of therapists' sessions with patients will be selected and stratified according to therapist and phase of the intervention in terms of early, mid or end sessions so that rating of therapy by an accredited member of the British Association of Behavioural and Cognitive Psychotherapists can be made. Ratings of therapy will be done using the Cognitive Therapy Scale (Young and Beck, 1980) which is a reliable measure of delivery of CBT (Vallis et al, 1986).

Therapist supervision and workload

Weekly supervision is a prerequisite of practice and audio-recordings of all therapy sessions is routinely made. Although supervision structures are well set up in IAPT, Prof Moorey, Dr Mannix and Dr Serfaty will be available to discuss any difficulties related to interventions in cancer patients.

We anticipate that 2 IAPT therapists will be required from each PCT to treat 4.5 patients per year each. We have already have experience in delivering a training programme for palliative care nurses in CBT skills (Mannix et al, 2006), which improves confidence in managing patients (Cort et al, 2009). Mannix, Moorey and Serfaty will extract and adapt relevant sections of this so that CBT therapists may adapt their skills to advanced cancer patients.

Treatment as Usual (TAU)

All patients will receive TAU from oncology teams and from their GPs. This consists mainly of routine support, such as appointments with GPs, clinical nurse specialists, oncologists and palliative care clinicians. The patient's physical health and medication will be reviewed and treatment modified according to symptoms such as pain. Psychotropic medication will be prescribed as necessary by either the patient's GP or oncologist. In line with NICE guidance specific psychological support may be available for those who present with psychological needs at any time and study participants will not be exempt from receiving external psychological support. We will however discourage specific psychological interventions aimed at treating symptoms of depression (e.g. CBT or Interpersonal Psychotherapy), but ultimately we cannot interfere with usual care. We will record the numbers of people receiving any psychological therapy during the trial, though in practice the numbers are likely to be small (Serfaty et al, 2009).

Qualitative work

PhD

There are high levels of distress in carers of people with advanced cancer, with levels of moderate to severe depression being as high as 15% at the advanced stage of disease (Burridge et al, 2009). We shall apply for separate funding for a PhD studentship to study this aspect of the trial. Our departments have been extremely successful in attracting both internal and external research funding for high quality candidates for PhDs. Once the main project is funded by the HTA, potential funding from MRC, NIHR and the Universities will be explored. The PhD will be an interview based study of a sample of informal carers of trial participants in order to understand more about the physical, social, psychological and economic burdens they encounter.

Patient Experience of CBT

We will conduct qualitative research to explore, with participants who have received Cognitive Behavioural Therapy (CBT) from the CanTalk trial, what they thought about the therapy, the therapist, how it's affected their quality of life and any suggestions they have for the future. This work complements the CanTalk study, and by looking at the experiences of a participant's therapy qualitatively we hope to gain a more detailed, in depth view than would be achieved using quantitative methods.

Existing Research

Although there is some evidence to suggest that CBT is an effective treatment for patients with depression and advanced cancer (Savard, Simard, Giguere et al. 2006), little is known about how patients in this group perceive CBT, their thoughts and experience of it.

The experience of cancer patients attending group CBT has been positive, with qualitative research having found that patients enjoy the interpersonal and social environment of the group (Edelman, Lemon and Kidman, 2005) and learn skills to challenge and solve problems (Bottomley, 1998). Feedback from patients receiving individual CBT has also been encouraging. Omylinska-Thurston and Cooper (2013) conducted qualitative interviews with eight patients with primary cancers who had received a course of psychological therapy within a NHS service for cancer patients and found that participants found talking about their feelings to someone outside their family and problem solving helpful. Cancer patients with metastatic disease in an additional study (conducted in Australia) also commented that CBT allowed them to share their thoughts and feelings with an understanding, caring therapist (Maccormack, Simonian, Lim, Redmond, Roets, Dunn and Butow, 2001). Finally, Anderson, Watson and Davidson (2008) found that hospice patients reported CBT to be acceptable and effective.

Although qualitative work has been conducted to explore cancer patients experience of individual CBT, there is a dearth of information about the experience of advanced cancer patients who receive CBT from the IAPT service in the UK. In IAPTs Four Year Plan of Action (2011) they aim to expand services to patient with chronic health conditions, including cancer. A report by the London Cancer Allicance (2014) has identified some reservations about the suitability of IAPT for treating chronic cancer patients. This study aims to address some of these concerns and explore what aspects of CBT participants found helpful, their thoughts of their therapist, the impact of CBT on their quality of life and what they think the best way to emotionally support cancer patients is.

Methods

Design

We will use purposive sampling and write to participant from the CanTalk trial who received CBT. We will conduct semi-structured, one to one interviews using a topic guide to ensure all participants are asked the same questions and to minimise researcher effects. A Semi-structured interview technique will be used with a loose structure and open ended questions. This will allow the interviewer or interviewee to divert from these questions to pursue other areas where necessary (Britten 1995). Interviews will take place in the participants' home or within the department where the research is taking place. The interviews will be in a place where there are minimum distractions for the participant and for the researcher to aid the dialogue. All interviews will be audio recorded for transcription at a later date. Data will be analysed using thematic analysis.

Interview schedule/topic guide

Patton (1987) suggested that there are six types of questions that can be asked during interviews:

- Experience/Behaviour Questions
- Opinion/Belief Questions

- Feeling Questions
- Knowledge Questions
- Sensory Questions
- Background/Demographic Questions

The topic guide was structured around these six types of question and covers questions about the therapist, the therapy, quality of life, overall thoughts of the therapy and suggestions for improvement.

Participants:

The study will recruit participants who have participated in the CanTalk study and have been randomised to the CBT arm of the study. These participants will have received up to 12 one hour sessions of CBT.

Method of recruitment:

Participants will be recruited into the trial in one of two different ways depending on when they were consented into the main CanTalk trial.

Method 1**.** Participants who have finished the treatment phase of the CanTalk study and signed the original consent form version 3 (which did not ask them whether they would be happy to be contacted about further research) will be approached in the first instance by a member of their clinical team via post. They will be send an invitation letter (Letter of Invitation_2) with consent to contact slip attached and full patient information sheet. Participants who indicate that they are happy to be contacted about the study will then be given a telephone call by a member of the CanTalk research team to discuss the study further.

Method 2. Participants who have signed the consent form version 4 (which included the question 'I am happy to be contacted about research in the future') will be sent an invitation letter (Letter of Invitation_1) and a patient information sheet by the research team. Participants who indicate they are interested in taking part will then be contacted by a member of the research team. Prior to sending out this letter a member of the CanTalk team will check with the patients clinical key worker that they have not deceased and that it is inappropriate to contact them.

Response rates:

It is predicted that CanTalk will recruit a total of 240 participants into the trial and around 120 will be randomised to the CBT arm. We will invite all participants recruited from sites in London who have completed the CanTalk study (i.e. reached the 24 week follow-up point), excluding those who have died or withdrawn from the study. We aim to interview 20 participants or until we are satisfied data saturation has been achieved, with no new themes emerging from the interviews.

Consent:

Full consent will be taken from all participants prior to interviews taking place. The consent form will inform participants that all interviews will be audio recorded for analysis at a later date.

Participant inclusion criteria:

Participants who were randomised to the CBT arm of the CanTalk trial and received CBT will be eligible for this study. To take part in this study, participants must also be able to give consent.

Sample size:

The study aims to recruit around 20 participants from the CanTalk trial to take part in this qualitative research. This should be a sufficient number to generate themes from the data.

PROJECT MANAGEMENT

Insurance

We do not foresee any difficulties with this trial however University College London holds insurance against claims from participants for injury caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept responsibility for any breach in the hospital's duty of care, or any negligence in the part of the hospital's employees. This applies whether the hospital is an NHS Trust or otherwise.

Hospitals selected to participate in this clinical trial have clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary can be provided on request.

Research Governance

The nominated sponsor is University College London. There will be a trial steering Committee (TSC) which consists of an independent chair (Dr Jackie Newby, Consultant Oncologist, Royal Free and North Middlesex Hospitals, London), at least two other independent members (to be appointed), the chief investigator and one other investigator plus user representative. Observers from the HTA programme will be invited to all TSC meetings.

There will be a separate Data Monitoring and Ethics Committee (DMEC) reporting to the TSC which will consist of a clinician and a statistician, to ensure that no harm results from the intervention and that numbers are being achieved.

The TSC and DMEC will meet once before the start of a trial (month 3), then twice during the pilot stage (Month 9 and 12), then 6 monthly until the last follow-up (months 18, 24, 30).

There will also be a Trial Management Group that consists of the Chief Investigator, co-applicants and trial manager and statisticians that meet at least three times a year and by telephone-conference as necessary to discuss the progression and day to day management issues of the trial. The chief investigator will be responsible for the overall leadership, management and outputs of the study and will maintain a log of the key milestones to be achieved against a timetable. The trial manager will be responsible for the day to day running and coordination of the study and will be accountable to Dr Serfaty (chief investigator). The management role will include obtaining ethics and

research governance approval, coordinating the collection of data, preparation of meetings and assisting with the writing and execution of the procedures and policies for the trial and disseminating the study's findings. The manager will also be responsible for ensuring recruitment is on target by collating monthly reports from each site researcher and reporting this to the PI and site leads. The site researchers in oncology clinics will be supervised by the trial manager and will be responsible for recruitment and assessment from oncology clinics. Ms Jo Burns, will be responsible for managing PCRN staff who will be recruiting from primary care and following up all patients. She will liaise closely with the research manager and Dr Serfaty (CI) to ensure satisfactory progress of the trial.

Recruitment Rate

We have chosen more conservative estimates for prevalence rates of major depressive disorder, than suggested in the research brief. One third of patients will be recruited from 66 GP practices and two thirds from oncology services; we wish to recruit 240 patients over 24 months (roughly 10 per month); 160 from oncology clinics (6.6 per month) and 80 from General Practices (3.3 per month). Although there may be some overlap with the patients identified from the same source, these numbers are likely to be small. The main constraints are those limited by service provision through IAPT, so that interventions can be absorbed into existing services. We will test the feasibility of recruitment by monitoring the project in the first 6 months. Although it needs to be acknowledged that recruitment may be slower at the start of the project we would suggest that 10 patients per month in total for the first 6 months would seem reasonable. We have provision to expand the study to include oncology clinics attached to the South London cancer network and use more general practices if necessary.

Timetable

Months	**1-3**	**4-6**	**7-9**	**10-12**	**13-15**	**16-18**	**19-21**	**22-24**	**25-27**	**28-30**	**31-33**	**34-36**	**37-39**	**40-42**
Orientation														
Recruitment			Pilot	Pilot										
Intervention			Pilot	Pilot										
Follow-up														
Analysis														
Write up														

Project Milestones

Date	Milestones
July – Dec 2011 (Months 1-6) Setting up of project: (6 months)	Advertise and appoint clinical trial manager and 2 research assistants for London. Apply for ethics and research governance approval for all sites and apply for banding with the NCRN. Purchase equipment. Registration of the projects with ISRCTN, Clincialtrials.gov Develop procedures and policies for the conduct of the trial. Complete the trainer for trainers manual for CBT in cancer. Modify telephone CBT manual for use in cancer patients. Conduct training in CBT for IAPT therapists and disseminate training manual. Conduct and supervise pilot treatment of 2 patients with advanced cancer with therapists. Conduct training for Oncology clinic NCRN staff and researchers and PCRN staff to undertake baseline and follow up assessments. Update literature. Appoint members to the trial steering committee and DMEC.
Jan 2012 – June 2012 (Months 7-12) Feasibility stage (6 months)	Recruitment and treatment of patients across all participating sites. Demonstrate recruitment and intervention is feasible. This stage will generate preliminary data on attrition and recruitment from different sources; oncology clinics and GP practices. It will enable us to make adjustments where necessary.
July 2012 – Dec 2013 (Months 13- 30) Ongoing trial (18 months)	Recruitment, intervention and follow up of patients.
Jan 2014 – March 2014 (Months 31-33) Completion of intervention (3 months)	Intervention phase and follow-up.
April 2014 – June 2014 (Months 34-36) Completion of main trial (3 months)	Complete final 3 month follow up data collection and entry. Close data base.
July 2014 – Sept 2014 (Months 37-39)	Data cleaning. Break blindness. Statistical and economic analysis. Rate CBT tapes using cognitive therapy scale. Discuss

Analysis of data, rate therapy, update literature search. (3 months)	findings with research team. Update literature search.
Oct 2014 – End Jan 2015 (Months 40-42) Dissemination and write up (3 months) End date: Jan 2015	Write up of complete study findings. Offer results to surviving study participants. Present findings at National and International conferences. Use conference feedback to prepare final report. Prepare report for funders and information to be placed on HTA web site. Complete paper for publication in peer reviewed journal.

Contribution of each member of the team

All the applicants have been involved in the design of the trial and development of the project.

Dr Serfaty is a Senior Lecturer and Consultant in Psychiatry as well as a CBT therapist/supervisor who will lead the team. He has led on large, multicentre trials of CBT and will use his expertise to liaise closely with all team members to ensure the smooth running of the trial. He will also provide training for IAPT therapists and be available for consultation should this be necessary. He will be involved with the analysis, write up and dissemination of the project.

Prof King is Professor of Primary Care, UCL, who is Head of Mental Health Sciences at UCL and joint Head of PRIMENT Clinical Trials Unit. He will help ensure the smooth running of the trial. He will assist with ensuring that recruitment is successful and help solve problems which may arise. He will also provide an input into the analysis and write up.

Dr Mannix is a palliative care consultant and CBT therapist. She will be involved with the development of the training manual and training for IAPT therapists. She will also be available for consultation should there be questions about managing patients with advanced cancer.

Prof Nazareth is Professor of Primary Care, UCL, Director of the MRC GPRF(to be rebranded) and joint Head of PRIMENT Clinical Trials Unit. He will contribute to the trial by helping ensure that recruitment and follow-up of all patients is successful. He will also provide trial expertise and will contribute to the write up and dissemination of the project.

Dr Jones is the Head of Marie Curie Palliative Care Research Unit (MCPCRU) at UCL. Marie Curie Cancer Care (MCCC), the largest non statutory provider of palliative care in the UK and its research unit is a leader in the field. She has wide experience in cohort and trial research in palliative care. She will help with NCRN badging, liaise with cancer and palliative care networks to ensure successful recruitment from cancer and related services. She will contribute to supervision of an externally funded PhD student, recruited to undertake qualitative research. She will also help to the write and dissemination of findings.

Dr Tookman is a palliative care physician with strong research interests and experience who is Director of Medical Specialities Royal Free Hampstead NHS Trust. He will help liaise with oncologists and palliative care physicians and also help with write up of the trial.

Dr Pilling is a psychologist who is joint director of the National Collaborative Centre for Mental Health. He will help liaise with IAPT services, to ensure the smooth delivery of CBT and help with the write up and dissemination of the trial.

Mr John Wood is a principle research associate and senior medical statistician based PRIMENT, UCL's clinical trials unit and he will help with the analysis and write up of the trial.

Mr Jeff Round Jeff Round is a principal research associate in the UCL Clinical Trials Unit and leads the health economics work of the unit. He will assist Anna Buylova (health economist) with the economics analysis and Markov modelling. She will also provide an input into the write up of the economic aspects of the trial.

Prof Luker is had of the School of Nursing, Midwifery and Social Work at the University of Manchester, head the Primary Care Research Group and is programme leader of the Macmillan research group. She will liaise with IAPT therapists in Knowsley. She will also help with the application for an externally funded PhD studentship who will undertake qualitative research and provide them with supervision.

Prof Moorey is the head of psychotherapy for the South London and Maudsley NHS Foundation Trust. He is a specialist in CBT for cancer and actively involved in IAPT. He will help develop the manual to train IAPT therapists in CBT, be involved in supervision where necessary and also help with the write up and dissemination of the trial.

Contribution of collaborators

Ms Marilyn Jones is a lay representative and member of the North London Cancer Network Cancer Patient Group. She will attend steering group meetings and provide an input into the development of material, such as information sheets, and also attend steering groups. She will also provide an opinion on the write up of the findings.

We are also collaborating with SURF, north London mental health user's group (see below) and **Ms Caren Watson,** their representative will continue to contribute to the progress of the study. **Mr Leurent** is a statistician who will help set up data bases and contribute to the analysis and write up for the trial.

Mr Singh is a cognitive behaviour therapist who has extensive experience in the development of IAPT. He will be involved in delivering therapy to a selection of clients and will also provide feedback on the IAPT training.

Ms Sarah Davis is a research nurse who will be involved in the design, coordination and administration of the trial.

Supervision arrangements for junior staff involved

The Clinical trials manager: will be supervised by Dr Serfaty with an input from Profs King and Nazareth. *The researchers* who are recruiting from oncology centres will be supervised by Dr Serfaty. *PCRN staff* will be supervised through the well established structure of supervision set up by the PCRN.

IAPT therapists: Weekly supervision is well developed for therapists delivering treatment in the IAPT programme. Therapists are routinely supervised using either audio or videotape feedback. We are using existing IAPT structures to demonstrate that findings from this trial are generalisable and can be rolled out across the UK within the existing IAPT framework. Prof Moorey and Drs Mannix and Serfaty will be available for consultation by IAPT therapists specifically during the course of the trial to ensure good practice and Governance.

Input from an accredited clinical trials unit

PRIMENT Clinical Trials Unit will organise the setting up of data bases, the web based randomisation, analysis and write up of the trial.

Service user involvement

User representative

Marilyn Jones is a service user with cancer who has been present at all the planning group meetings during the preparation of this brief and advised on trial methodology. She suggested that the MINI was preferable to the CIDI because of the length of time the latter took to complete in a potentially vulnerable population. It was also suggested that consent to participate in the trial should be sought prior to conducting the more lengthy interviews, so as to minimise potential participants time. Ms Jones will continue to attend all steering committee meetings and provide an input during the course of the project.

User group

The Camden and Islington Service User Research Forum (SURF) has been actively involved in the preparation stage. This is an organisation supported by the member organisations of the Camden and Islington Mental Health Service Evaluation Partnership (Camden and Islington Mental Health and Social Care Trust, Islington PCT, Camden PCT and University College London) whose members are service users living in Camden, Islington and other parts of North London and who have an interest or experience in working in mental health research. Their users helped shape the project and will also continue to support and encourage PCTs to continue to ensure that IAPT therapies are available for people with advanced cancer and depression in primary care. Ms Caren Watson, a former user of mental health services, will continue to attend steering group meetings and act on behalf of SURF.

COSTS

Justification of support required

Staff

A: Employed through UCL: We have budgeted for (a) *A trial manager (co-ordinator)* (grade 8) for the whole trial to help with setting up of the project, liaise with researchers and PCRN staff. He/she

will also be involved with updating of the literature, data collection and entry and liaise with the statisticians for analysis. The research coordinator will also be involved with write up and help with dissemination of results. (b) *Two research assistants* (grade 6B) will assist the trial coordinator by assessing and consenting and taking measures of outcome from patients referred from oncology clinics. They will start 3 months prior to recruitment and finish 3 months post follow-up to help with data entry. (c) *A half time research administrator*: To help liaise with clinic staff and the PCRN staff. To help with general administration including setting up of contracts, photocopying, letters, invoicing, taking calls.(d) Senior staff: Dr Serfaty (8 hours), Prof King (2 hours) and Prof Pilling (1 hour). Although no direct costs are incurred for Dr Jones (2 hours)and Ms Holman (1 hour), who are employed through UCL and funded directly through a core grant from Marie Curie Cancer Care, estates and indirect costs will be incurred. .

B: Other HEI costs: Dr Sweeting, Dr Fernandez (1 hour each).

C: NHS Research costs: We have budgeting for the time (in hours weekly) for each of the co-applicants: Dr Mannix and Prof Luker (3 hours each); and Dr Tookman and S Moorey (2 hours each).

D: PCRN staff costs: The PCRN require staff time to help with co-ordination and training of research staff, collating data collected, liaising with UCL research staff. We have budgeted for staff research time to consult data bases to identify and screen primary care registers, to assess and consent patients for suitability of the trial and collect follow-up data. Prof Nazareth (1 hour), Baptiste Leurent (statistician) (2 hours).

Equipment

We have budgeted for 20 mini disc recorders at £120 each to record therapy sessions. We have also included four desktop computers at £900 each.

Travel

(a) We have budgeted for London zones 1-5 travelcards for the trial coordinator and research assistants. (b) We have costed £12 for the travel of patients for assessments and follow-up. (c) Travel for IAPT therapists for two training days every six months for two years and the cost and (d) accommodation for CBT trainers to go to Manchester to train IAPT therapists. (e) We have costed for travel of steering group members to meetings.

Consumables

(a) We have costed for project-specific stationery, printing, photocopying and three mobile phones for safety. (b) Minidiscs for quality control and supervision. (c) Sustenance for steering group meetings.(d) Software licences (£200 per computer) and copyrights for questionnaires (£20 per time point). (e) Library costs for updating literature and inter-library loans £1,125.

Other costs

(a) Recruitment costs £400 per post for four posts. (b) Ratings of tapes at £120 a tape; one in ten of an average of ten sessions for each of 94 patients. (c) We have costed for attendance at 14 steering group meetings at a cost of £35 per hour per user, which includes travel costs. (d) Randomisation costs: clinical trials unit to set up a web-based database £50,000 and web randomisation £4,000.

NHS Service Costs

We have budgeted for usual clinic staff time and clinic space in both oncology clinics and through the PCRN. We anticipate using 787 hours of clinic time and 582 hours of staff time. Ten minutes per patient will be required to check data bases on 2,573 people. Of these, 1,543 will be asked to agree to two screening questions (5 minutes) and we anticipate 1,286 will agree. Of these 288 patients will screen positive and be asked to read some background material (10 minutes). Our own researchers will subsequently assess 288 patients using the MINI (20 minutes each) in the clinic and also collect baseline data (33 minutes each).

NHS support costs

We anticipate that an average 120 patients will take up 9 out12 CBT sessions offered. We have therefore budgeted for 1,080 CBT sessions to be delivered by mid level band 7 CBT therapists.

8. Figure 1. Flow diagram for people screened in CanTalk Study.

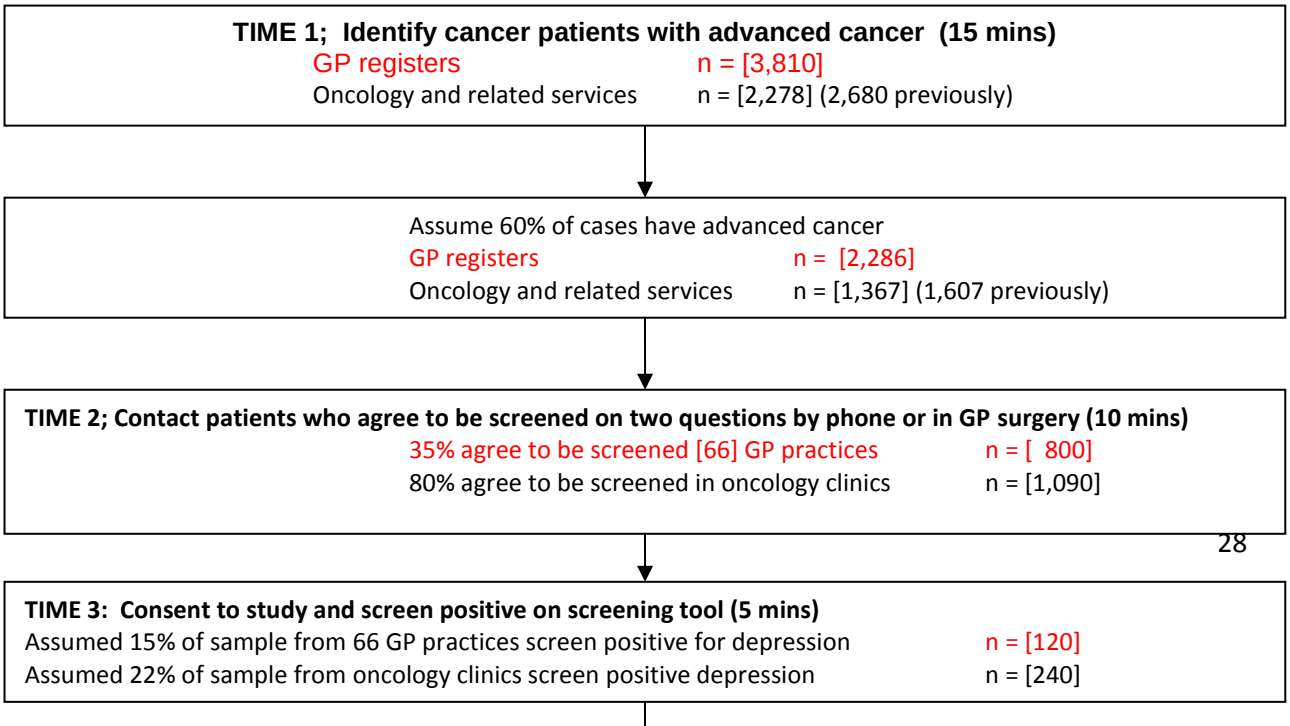
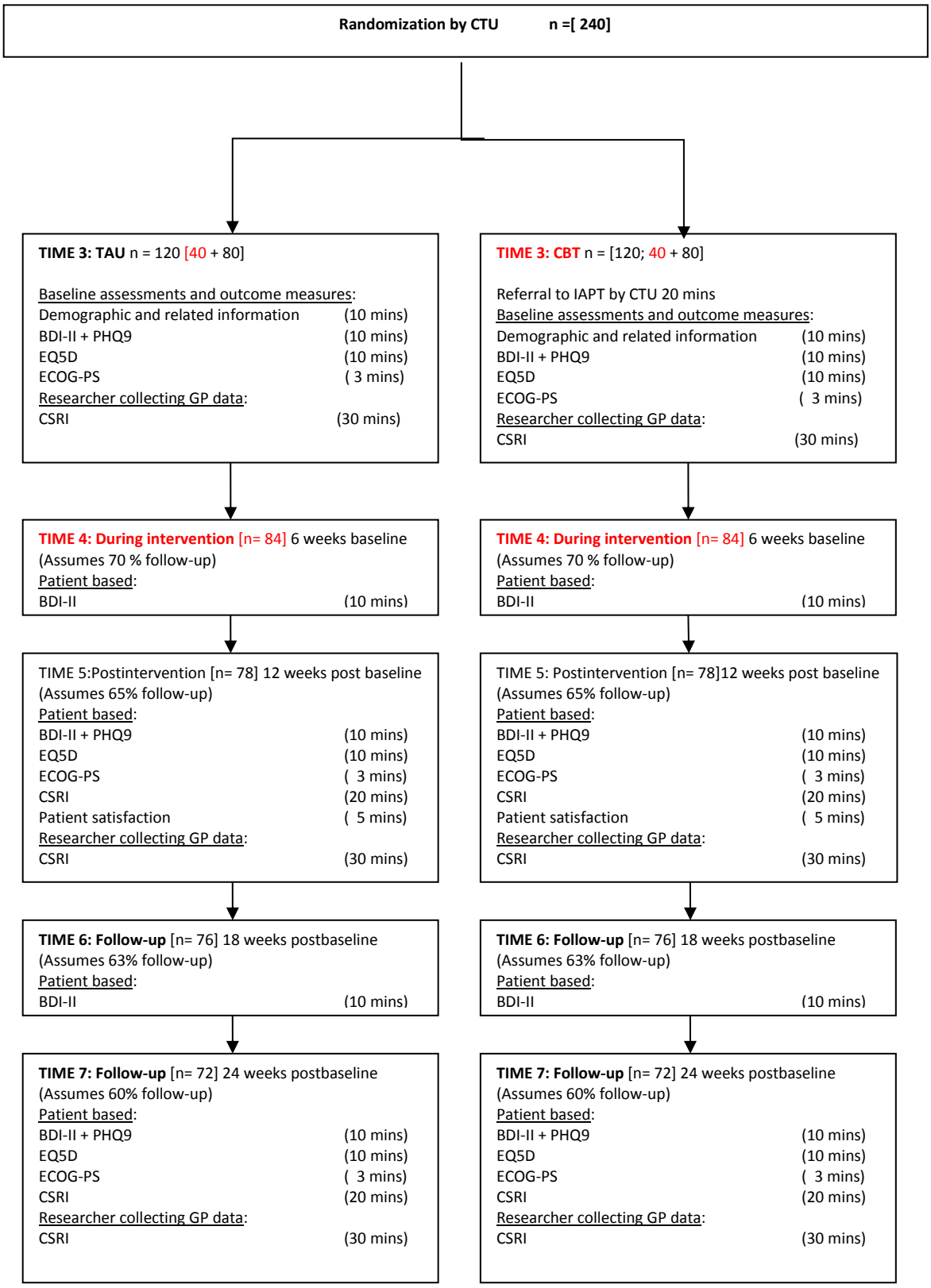


Figure 2. Flow diagram for people randomised into the CanTalk study.

TAU = Treatment as Usual CBT = cognitive Behaviour Therapy



References

Akechi T, Okuyama T, Onishi J, Morita T, Furukawa TA. Psychotherapy for depression among incurable cancer patients. Cochrane Database of Systematic Reviews, Issue 4, 2009.

Alexander PJ, Dinesh N, Vidyasager MS. Psychiatric morbidity among cancer patients and its relationship with awareness of illness and expectations about treatment outcome. Acta Oncol 1993; 32:623-626

Amorim P, Lecrubier Y, Weiller E, et al. DSMIII-R psychotic disorders: procedural validity of the Mini International Neuropsychiatric Interview (MINI). Concordance and causes for discordance with the CIDI. Euro Psych. 1998; 13: 26–34.

Anderson T, Watson M, Davidson R. The use of cognitive behavioural therapy techniques for anxiety and depression in hospice patients: a feasibility study. Palliative Medicine. 2008; 22:1-8.

Arroll B, Khin N, Kerse N Screening for depression in primary care with two verbally asked questions: cross sectional study. BMJ. 2003;327:1144-1146. doi:10.1136/bmj.327.7424.1144

Beecham JK, Knapp MRJ. Costing psychiatric options. In Thornicroft G, Brewin C, Wing JK (eds), Measuring Mental Health Needs. London: Gaskell. 1992.

Beck AT, Rush AJ, Shaw BF, Emery G. *The cognitive therapy of depression.*New York:Guilford Press; 1979.

Beck A, Steer R. Manual for the BDI-II. San Antonio: Psychological Corporation. 1996.

Beck AT, and Freeman A. Cognitive therapy for personality disorders. New York, NY: Guilford Press; 1990

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961; 4: 561-571.

Bowers and D.A. Boyle, Depression in patients with advanced cancer, *Clinical Journal of Oncology Nursing.* 2003; 7: 281–289.

Borkovec TD, Nau SD. Credibility of analogue therapy rationales. J Behav Ther Exp Psychiatry. 1972; 3: 257-260.

Bottomley A. Group cognitive behavioral therapy with cancer patients: the views of women participants on a short-term intervention. European Journal of Cancer. 1998; 7:23-30.

Britten N. Qualitative research: qualitative interviews in medical research. BMJ. 1995; 311:251-253.

Brooks R. EuroQol Group. EuroQol: the current state of play. Health Policy. 1996; 37: 53-72.

Burridge L, Barnett A, Clavarino A. The impact of perceived stage of cancer on carers' anxiety and depression during the patients' final year of life. Psychooncology. 2009; 18(6): 615-23.

Campbell H, Sanson-Fisher R, Taylor-Brown J, Hayward L, Wang S, Turner D. The Cancer Support Person's Unmet Needs Survey. Cancer (15th July) DOI: 10.1002/cncr.24386, www.interscience.willey.com. 2009.

Carlson LE, Bultz BD. Efficacy and medical cost offset of psychosocial interventions in cancer care: making a case for economic analyses. Psychooncology. 2004; 13: 837-849

Chiles J, Lambert MJ, Hatch AL. The impact of psychological interventions on medical cost offset: a meta-analytic review. Clinical Psychology Science and Practice. 1999; 6: 204-220.

Cort E, Moorey S, Hotopf M, Kapari M, Monroe B, Hansford P. Palliative care staff experiences of training in cognitive behaviour therapy and taking part in a randomized controlled trial. Int J Palliat Nurs. 2009;15(6):290-8.

Csipke E, Serfaty M, Buszewicz M. Optimizing recruitment from primary care: methods of recruiting older people with depression. Primary Health Care Research & Development. 2006; 7(2): 116-123.

Cunningham AJ, Edmonds CV, Jenkins GP, Pollack H, Lockwood GA, Warr DA. A randomized controlled trial of the effects of group psychological therapy on the survival of women with metastatic breast cancer. Psychooncology 1998;7:508-17.

Curtis. Unit costs of health and social care 2008. Canterbury: Personal Social Services Research Unit.

Department of Health (2011). Talking therapies: A four-year plan of action. Available from URL: https:// www.gov.uk/government/uploads/system/uploads/attachment_data/file/213765/dh_123985.pdf accessed December 18, 2014

Drabe N, Zwahlen D, Buchi S, Moergeli H, Zwahlen RA, Jenewein J. Psychiatric morbidity and quality of life in wives of men with long-term head and neck cancer. Psycho-Oncology. 2008; 17: 199-204.

Drummond M, Sculpher M, Torrance G, et al. Economic evaluation using decision analytic modelling (Chapter 9). In Methods for the Economic Evaluation of Health Car Programmes. 3rd Ed. Oxford University Press. 2005.

Edelman S, Bell DR, Kidman AD. A group cognitive behaviour therapy programme with metastatic breast cancer patients. Psychooncology. 1999; 8: 295–305.

Edelman S, Lemon J, Kidman A. Group cognitive behaviour therapy fo breast cancer patients: a qualitative evaluation. Psychology, Health and Medicine. 2005; 2: 139-144.

Edwards AG, Hulbert-Williams N, Neal RD. Psychological interventions for women with metastatic breast cancer. Cochrane Database Syst Rev. 2009 Jul 16;(4):CD004253.

EuroQol Group, EuroQol—A new facility for the measurement of health-related quality of life. Health Policy.1990; 16: 199–208.

Furukawa TA, McGuire H, Barbui C. Meta-analysis of effects and side effects of low dosage tricyclic antidepressants in depression: systematic review. British Medical Journal. 2002; 325: 1-9.

Gandubert C, Carriere I, Escot C, Soulier M, Hermes A, Boulet P, Ritchie K, Chaudieu I.Onset and relapse of psychiatric disorders following early breast cancer:a case-control study. Psycho-Oncology. 2009;18: 1029-37.

Goodwin PJ, Leszcz M, Ennis M, et al The effect of group psychosocial support on survival in metastatic breast cancer. N Engl J Med 2001;345:1719-1726.

Harrington J, Barlow C, Ornadel K, Drake R, King M, Jones L. Advance care planning in advanced cancer: can it be achieved? A randomised controlled preference trial of a care planning discussion. Abstract from poster B134. National Cancer Research Institute. 2009.

Hotopf M, Chidgey J, Kelly L, Addington-Hall, J. Depression in advanced disease – a systematic review: prevalence and case finding. Palliative Medicine. 2002; 16: 81-97.

Hutchinson SA, Wilson ME, Skodal Wilson H. Benefits of Participating in Research Interviews. Image: the Journal of Nursing Scholarship; 26: 161–166

Jordhøy MS, Kaasa S, Øvreness T, Underland G, Ahlner-Elmqvist M. Challenges in palliative care research; recruitment, attrition and compliance: experience from a randomized controlled trial. Palliative Medicine. 1999; 13: 299–310.

Kamboj SK, Tookman A, Jones L, Curran HV. The effects of immediate-release morphine on cognitive functioning in patients receiving chronic opioid therapy in palliative care. Pain. 2005;117:388–395.

Kessler D, Lewis G, Kaur S, Wiles N, King M, Weich S, Sharp DJ, Araya R, Hollinghurst S, Peters TJ. Therapist-delivered internet psychotherapy for depression in primary care: a randomised controlled trial. Lancet 2009; 374: 628–3

King M, Jones, L, Richardson A, Murad S, Irvin A, Haslett H, Ramsay A, Coelho H, Andreou P, Tookman A, Mason C, Nazareth I. The relationship between patients' experiences of continuity of cancer care and health outcomes: a mixed methods study. British Journal of Cancer. 2008; 98: 529-536.

King M, Lones L, McCarthy O, Rogers M, Richardson A, Williams R, Tookman A, Nazareth I. Development and pilot evaluation of a complex intervention to improve experienced continuity of care in patients with cancer. British Journal Cancer 2009; 100:274-280.

King M, Davidson O, Taylor F, Haines A, Sharp D, Turner R. Effectiveness of teaching general practitioners skills in brief cognitive behaviour therapy to treat patients with depression: randomised controlled trial. BMJ. 2002; 324: 1-6.

Koopman C,Hermanson K,Diamond S, Angell K, Spiegel D. Social support, life stress, pain and emotional adjustment to advanced breast cancer. Psycho-oncology 1998;**7**:101–111.

Kroenke K, Spitzer RL. The PHQ-9: A new depression and diagnostic severity measure. Psychiatric Annals. 2002; 32: 509-521.

Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. Journal of General Internal Medicine. 2001; 16(9): 606-613.

Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two item depression screener. Medical Care. 2003. 41: 1284-92.

Laidlaw T, Bennett B, Dwivedi P, Naito A, Gruzelier J. Quality of life and mood changes in metastatic breast cancer after traiing in self-hypnosis or Johrei: a short report.. Contemporary hypnosis 2005;**22**(2):84–93.

Lecrubier Y, Sheehan D, Weiller E, Amorim P, Bonora I, Sheehan K, Janavs J, Dunbar G. The MINI International Neuropsychiatric Interview (M.I.N.I.) A Short Diagnostic Structured Interview: Reliability and Validity According to the CIDI. European Psychiatry. 1997; 12: 224-231.

Lemieux J, Topp A, Chappell H, Ennis M, Goodwin J. Economic analysis of psychosocial group therapy in women with metastatic breast cancer. Breast Cancer Res Treat. 2006; 100: 183-190.

LinnM, Linn B, Harris R. Effects of counselling for late stage cancer patients. Cancer 1982; 49:1048–1055.

Lloyd-Williams M, Shiels C, Taylor F, Dennis M. Depression — An independent predictor of early death in patients with advanced cancer. Journal of Affective Disorders. 2009; 113: 127–132.

London Cancer Alliance (LCA) West and South. Developing a pathway for mental health and psychological support services for adults. Available from URL: http://www.londoncanceralliance.nhs.uk/media/83191/developing-a-pathway-for-mental-health.pdf [accessed December 18, 2014].

Low J, Gessler S, Williams R, Daniells E, Brough V, Tookman A, Jones L. Screening for distress and depression in cancer patients: is ultrashort depression screening a valid measure in the UK? A prospective validation study. J Pain Symptom Manage. 2009 Aug;38(2):234-43. Epub 2009 Apr 2.

Maguire P. (1985) Improving the detection of psychiatric problems in cancer patients. Social Science and Medicine 20, 819–823.

Mahoney FI, Barthel D. Functional evaluation: the Barthel Index. Maryland State Med J. 1965; 14: 56-61.

Mannix KA, Garland A, Gracie J, Moorey S, Reid B, Standart S, Scott J. Effectiveness of brief training in cognitive behaviour therapy techniques for palliative care practitioners. Palliative Medicine 2006;20:579-584.

McDaniel JS, Musselman DL, Porter MR, Reed DA, Nemeroff CB (1995): Depression in patients with cancer. Diagnosis, biology, and treatment. *Arch Gen Psychiatry* 52:89–99.

Moorey S and Greer S. Psychological Therapy for Patients with Cancer: A New Approach. 1989. Heinemann Medical Books, Oxford.

Moorey S, Greer S, Watson M. Adjuvant psychological therapy for patients with cancer. *Psycho-Oncology* . 1994;7:218-228.

Moorey S. When bad things happen to rational people: cognitive therapy in adverse life circumstances. In: Salkovskis PM, editor. Frontiers of cognitive therapy. New York: The Guildford Press; 1996.

Moorey S, Cort E, Kapari M, Monroe B, Hansford P, Mannix K, Henderson M, Fisher L, Hotopf M. A cluster randomized controlled trial of cognitive behaviour therapy for common mental disorders in patients with advanced cancer. Psychological Medicine 2009: 39: 713–723.

Nezu AM, Ronan GF, Meadows EA, McClure KS. Practitioner's Guide to Empirically Based Measures of Depression New York. Kluwer Academic/ Plenum Publishers. 2000.

National Institute of Clinical Excellence. Improving supportive and palliative care for adults with cancer. The manual. Guidance on cancer Services. ISBN 1-84257-579-1. 2004.

Maccormack T, Simonian J, Lim J, Redmond L, Roets D, Dunn S, Butow P. "Someone Who Cares:" A qualitative investigation of cancer patients' experiences of Psychotherapy. Psycho-Oncology. 2001; 10:52-65.

McLean LM, Jones JM, Rydall AC. A couples intervention for patients facing advanced cancer and their spouse and caregivers: outcome of a pilot study. Psycho-oncology. 2008; 16: 277-286.

Manzanera C, Lafay N, Papet N, Senon JL. Depression, anxiety, and cancer. Annales Medico-Psychologiques. 2003; 161: 140-146.

Massie MJ. Prevalence of depression in patients with cancer. Journal of the National Cancer Institute Monographs. 2004; 32: 57-71.

McNair DM, Lorr M, Droppleman LF. Profile of Mood States. Edits / educational and industrial testing service, San Diego, California 92167. 1992.

Mitchell AJ. Are one or two simple questions sufficient to detect depression in cancer and palliative care? A Bayesian meta-analysis. British Journal of Cancer. 2008; 98: 1934-1943.

Muniz PS, Nardi AE, Campos FC. Psychiatric disorders in a palliative care unit. Abstract for poster sessions / European Psychiatry. 2007; 22: 221-341.

Newell SA, Sanson-Fisher R, Savolainen NJ. Systematic Review of Psychological Therapies for Cancer Patients: Overview and recommendations for Future Research. J National Cancer Institute. 2002; 94: 558-84.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5: 649-655.

Omylinska-Thurston J, Cooper M. Helpful processes in psychological therapy for patients with primary cancers: a qualitative interview study. Counselling and Psychotherapy Research. 2014; 2:84-92.

Osborn RL, Demoncada AC, Feuerstein M. Psychosocial interventions for depression, anxiety and quality of life in cancer survivors: meta-analyses. International Journal of Psychiatry in Medicine. 2006; 36: 13-34.

Passik SD, Kirsh KL, Theobald D, Donaghy K, Holtsclaw E, Edgerton S, Dugan W. Use of a depression screening tool and a fluoxetine-based algorithm to improve the recognition and treatment of depression in cancer patients: a demonstration project. J Pain Symptom Management. 2002; 24: 318-27.

Passik SD, Donaghy KB, Theobald DE, Lundberg JC, Holtsclaw E, Dungan WM. Oncology staff recognition of depressive symptoms on videotaped interviews of depressed cancer patients: Implications for designing a training program. Journal of Pain and Symptom Management. 2000; 19: 329-338.

Passik SD, Kirsh KL, Donaghy KB, Theobald DE, Lundberg JC, Holtsclaw E, Dugan WM. An attempt to employ the Zung Self-Rating Depression Scale as a "lab test" to trigger follow-up in ambulatory oncology clinics: Criterion validity and detection. Journal of Pain and Symptom Management. 2001; 21: 273-281.

Patton MQ. How to use qualitative methods in evaluation. Newbury Park, California: SAGE Publications, Inc. 1987.

Pessin H, Olden M, Jacobson C, Kosinski A. Clinical assessment of depression in terminally ill cancer patients: A practical guide. Palliative & Supportive Care. 2005; 3: 319-324. doi:10.1017/S1478951505050480

Pinto-Meza A, Serrano-Blanco A, Penarrubia MT, Blanco E, Haro JM. Assessing depression in primary care with the PHQ-9: can it be carried out over the telephone? J General Internal Medicine. 2005; 20(8): 738-42.

Potash M, Breitbart W. Affective disorders in advanced cancer. Hematology/oncology clinics of North America. 2002; 16(3): 671-700

Price A, Hotopf M. The treatment of depression in patients with advanced cancer undergoing palliative care. Current opinion in supportive and palliative care. 2009; 3: 61-6.

Reeve J. Understanding distress in people with terminal cancer. PhD thesis. Liverpool: Liverpool University. 2006.

Reeve JL, Lloyd-Williams M, Dowrick C. Revisiting depression in palliative care settings: the need to focus on clinical utility over validity. Palliat Med. 2008; 22(4): 383-91

Reeve J, Lloyd-Williams M and Dowrick C. Depression in terminal illness: the need for primary care-specific research. Family Practice 2007; Pages 1–6 of 6

Rosenberg HJ, Rosenberg SD, Ernstoff MS, Wolford GL, Amdur RJ, Elshamy MR, Bauer-Wu SM, Ahles TA, Pennebaker JW. Expressive disclosure and health outcomes in a prostate cancer population. Int J Psychiatry Med. 2002; 32: 37-53

Saunders, JB, Aasland, OG, Babor, TF, De La Fuente, J. and Grant, M. (1993) Development of the Alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption II. *Addiction* 88 , pp. 791-804

Savard J, Simard S, Guiere I, Ivers H, Morin CM, Maunsell E, Gagnon P, Robert J, Marceau D. Randomized clinical trial on cognitive therapy for depression in women with metastatic breast cancer: psychological and immunological effects. Palliat Support Care. 2006; 4: 219-37

Semple CJ, Dunwoody L, Sullivan K, Kernohan WG. Patients with head and neck cancer prefer individualized cognitive behavioural therapy. European Journal of Cancer Care 2006; 15: 220-227

Serfaty MA, Haworth D, Blanchard M, Buszewicz M, Murad S, King M. Clinical effectiveness of cognitive behaviour therapy, versus control treatment or treatment as usual for depressed older people in general practice. Archives of General Psychiatry. 2009; 66: 1332-1340

Serfaty M, Wilkinson S, Freeman C, Mannix K, King M. *The ToT Study: Helping with Touch or Talk (ToT):* A pilot randomised controlled trial to examine the clinical effectiveness of aromatherapy massage versus cognitive behaviour therapy for emotional distress in patients in cancer/palliative care. (In preparation for publication following study funded by Dimbleby Cancer Care. Grant 6809)

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. Comparison of the Mini International Neuropsychiatric Interview (MINI) with the SCID-P and the CIDI: a validity study. Psychopharm Bull. 1995; 31: 616.

Sheehan D, Janavs J, Baker R, Harnett-Sheehan K, Knapp E, Sheehan M, Lecrubier E, Weiller E, Hergueta T, Amorim P, Bonora LI, Lepine JP, Mini International Neuropsychiatric Interview, English Version 5.0.0, DSM-IV. 1998.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998; 59 Suppl 20:22–33.

Simon G, Ludman EJ, Rutter CM. Incremental Benefit and Cost of Telephone Care Management and Telephone Psychotherapy for Depression in Primary Care. Arch Gen Psych. 2009; 66: 1081-89.

Simon GE, Ludman EJ, Tutty S, Operskalski B, Von Korff M. Telephone psychotherapy and telephone care management for primary care patients starting antidepressant treatment: a randomized controlled trial. JAMA. 2004; 292: 935-942.

Simpson JS, Carlson LE, Trew ME. Effect of group therapy for breast cancer on healthcare utilization. Cancer Pract. 2001; 9: 19-26.

Spiegel D, Bloom J, Kraemer H, Gottheil E. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. The Lancet 1989;2:888–891.

Spiegel D, Bloom J, Yalom I. Group support for patients with metastatic cancer. *Archives of General Psychiatry* 1981;38:527–533.

Spitzer R, Kroenke K, Williams J. Validation and utility of a self-report version of PRIME-MD: the PHQ Primary Care Study. Journal of the American Medical Association. 1999; 282: 1737-1744

Stiefel F, Die Trill M, Berney A, Olarte JMN, Razavi D. Depression in palliative care: a pragmatic report from the Expert Working Group of the European Association for Palliative Care. Support Care Cancer. 2001; 9: 477–488.

Strong V, Waters R Hibberd C, Murray G, Wall L, Walker J, McHugh G, Walker A, Sharpe M. Management of depression for people with cancer (SMaRT oncology 1): a randomised trial. Lancet. 2008; 372: 40–48.

Sukegawa A, Miyagi E, Asai-Sato M, Saji H, Sugiura K, Matsumura T, Kamijyo A, Hirayasu Y, Okamoto N, Hirahara F. Anxiety and prevalence of psychiatric disorders among patients awaiting surgery for suspected ovarian cancer. Journal of Obstetrics and Gynaecology Research. 2008; 34: 543-551.

Thekkumpurath P, Venkateswaran C, Kumar M, Bennett MI. Screening for psychological distress in palliative care: a systematic review. J Pain Symptom Manage. 2008;36(5):520-8.

Tutty S, Simon G, Ludman E. Telephone counseling as an adjunct to antidepressant treatment in the primary care system: a pilot study. Eff Clin Practice. 2000; 3: 170-178.

Vallis TM, Shaw BF, Dobson KD. The Cognitive Therapy Scale: psychometric properties. J Consult Clin Psychol. 1986; 54: 381-385.

Williams S, Dale J. The effectiveness of treatments for depression/depressive symptoms in adults with cancer: a systematic review. British Journal of Cancer. 2006; 94: 372-90.

Wilson KG, Chochinov HM, de Faye BJ, BreitbartW.Diagnosis and management of depression in palliative care. In: Chochinov HM, Breitbart W, eds. Handbook of psychiatry in palliative medicine. Oxford: Oxford University Press; 2000

Walsh K, Jones L, Tookman A, Mason C, Mcloughlin J, Blizard R, King M Reducing emotional distress in people caring for patients receiving specialist palliative care. Br J Psych (2007) 190: 142-147.

Ward E, King M, Lloyd M, Bower P, Sibbald B, Farrelly S, Gabbay M, Tarrier N, Addington-Hall J. Evaluation of non-directive counselling, cognitive-behaviour therapy and usual general practitioner care for patients with depression. I: Clinical Effectiveness. *BMJ*. 2000;321:1383-1388 .

Wood BC, Mynors-Wallis LM. Problem-solving therapy in palliative care. Palliat Med 1997;11:49–54.

Young J,Beck AT. Cognitive Therapy Scale: Rating Manual. Philadelphia,Pa: Center for Cognitive Therapy. 1980

Zwahlen RA, Dannemann C, Gratz KW, Studer G, Zwahlen D, Moergeli H, Drabe N, Buchi S, Jenewein J. Quality of life and psychiatric morbidity in patients successfully treated for oral cavity squamous cell cancer and their wives. Journal of Oral & Maxillofacial Surgery. 2008; 66: 1125-32.

Note:

This is not the original REC approved protocol. This has been adapted by the following:

- Formatting
- Synopsis added verbatim from text
- Amendments from original protocol added to text.

Original Protocol available on request.